

CORONARY HEART DISEASE IN YOUNG ADULTS
A MULTIDISCIPLINARY STUDY

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DEDICATED

*to the prolongation of the life
and to the protection of the health
of the young coronary candidate himself*

Preface

THIS monograph presents a summary of an interdisciplinary research on coronary heart disease begun in 1946 under the auspices of seven physicians. Four on the medical staff of the Massachusetts General Hospital Boston represented in particular the cardiovascular and metabolic fields. Drs. Edward F. Bland, Jacob Lerman, Howard B. Sprague and Paul D. White. The three others were Dr. Samuel A. Levine of the Peter Bent Brigham Hospital, Dr. Stanley M. Garn of the Department of Anthropology of Harvard University, referred to the project by Professor Ernest A. Hooton, chairman of that department and Dr. Fred Alexander, Assistant in Medicine at the Massachusetts General Hospital who carried out pilot examinations of the first twelve patients studied. During the first year the financial support came from the Cardiac Research Fund of the Massachusetts General Hospital. As plans developed and the research grew in scope it was necessary to assign a full time medical worker to the project and to seek aid to defray the mounting expenses. Happily Dr. Menard M. Gertler was available as full time director of the study. Dr. Garn was also able to devote much time and energy to it during more than two years. The Commonwealth Fund made a generous allocation to support the research from January 1, 1948 through May 1950 and to publish the present monograph. Valuable help has come through consultation, from Dr. James B. Hamilton, Professor of Anatomy, the State of New York Medical College, Brooklyn, N.Y. and from Dr. Alan M. Butler and Miss Margaret Rourke of the Laboratory Department of the Massachusetts General Hospital. We are also greatly indebted to Dr. John Poutas and to the executives of the Lever Brothers Company in Cambridge, Mass. for making available individual subjects for our unmatched and matched control study. To the executive staff of Filene's Department Store, Boston and to the medical staff, the authors are indebted for the cooperation given during the selection of additional individuals who were necessary to complete the matched control group. To Dr. John Fertig we are all very grateful for his generous advice and painstaking efforts in the final preparation.

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PAUL D. WHITE

*Boston, Mass.
March 1954*

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CORONARY HEART DISEASE IN YOUNG ADULTS
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CHAPTER I

Introduction The Problem and the Procedure

HEART disease due to coronary atherosclerosis is a major problem in the world today. Cardiovascular renal diseases now claim as their victims half of all those who die in the United States. The percentage reported by the Public Health Service for the United States Registration Area was 49.5 in 1948 and 52.0 in 1950—much greater than the sum of the deaths from the next four causes: cancer, accidents, tuberculosis and pneumonia. Although owing in large part to the steadily increasing control of infectious diseases, a greater number of persons now reach old age when cardiovascular diseases are prone to occur, there are still many thousands who die of heart disease in youth and middle age.

One of the most, perhaps *the* most important and common kinds of heart disease results from atherosclerosis of the coronary arteries. It is most surprising that relatively little intensive research has been carried out in the past concerning the etiology of this vitally important hazard to the life of man. Only a rare person like Dr. Timothy Leary of Boston had taken an active interest in the subject before the past few years when other worthwhile studies of the fundamental causes of the disease commenced to engage the interest and talents of serious workers. The present research we venture to believe is such a study, but even it, like several others in the field, has but scratched the surface, uncovering problems that need still deeper thought and study.

The background of the present study extends to 1937 when Glendy Levine and White published a report briefly analyzing 100 patients under the age of 40 who had coronary heart disease and comparing them with a group of healthy old persons. In the search for clues two important findings stood out: (a) there were 96 males and only 4 females in the coronary group out of a population having equal numbers of males and females and (b)

the majority of the patients were of husky that is mesomorphic build. Another interesting fact was that the healthy old people had had in youth many more infectious diseases such as diphtheria and typhoid fever, than had the coronary patients. Further study of these groups was prevented by preoccupation with World War II, but the problems continued to be turned over in the minds of the investigators as evidenced by the question asked by White in the third edition of his textbook *Heart Disease* published in 1944.

Why should the robust and apparently most masculine young male be particularly prone to this disease? Incidentally Levine in 1929 working with Brown had described the type of male especially subject to coronary thrombosis as short, thickset and obese with thick wrists.

On the basis of these earlier interests and because of the compelling challenge of this increasingly serious disease a new research study of coronary atherosclerosis in youth was organized as soon as postwar conditions permitted. Many clues which hung together loosely had been uncovered by previous studies on coronary heart disease. This project was conceived (a) to study more intensively the existing clues and (b) to unite in a more cohesive fashion the various disciplines from which these clues stemmed. Accordingly coronary heart disease was studied from the following viewpoints: sex selection and the morphological, genetic, athletic, occupational, physiological, psychological, clinical, dietary, hormonal and biochemical aspects.

It was obvious that the relation of sex to the problem needed to be studied further and it was for this reason that the advice and cooperation of Dr. James B. Hamilton were sought. Biochemical and metabolic studies were carried out in the laboratories of the Massachusetts General Hospital by Miss Margaret Rourke. Physical and psychological examinations, complete histories including the factor of diet, x-ray films and electrocardiograms were secured with the cooperation of all concerned. The question of heredity was also studied.

Selection of Patients

An upper age limit was set in the belief that the individual who had a coronary occlusion at an early age would show predisposing characteristics. The maximum age used by Glendy White and

TABLE 1-1 Sources of patient referrals to the coronary research project

	<i>No of patients</i>
Project advisors	27
M G H associated cardiologists	12
Out patient and house records	4
Self referral*	1
Referring cardiologists	36
Veterans Administration	20
TOTAL	100

Applied for the study following a newspaper description of the project.

Levine was retained 40 years or less at the time of myocardial infarction and less than 50 at the time of examination. The limit was set at 40 rather than 35 or 30 as a matter of convenience in obtaining enough patients. Although the youngest patient in the series was 22 at the time of his myocardial infarction, the majority (61 out of 97 males) had their myocardial infarction between the ages of 35 and 40.

Patients were accepted for study in the Coronary Research Project only if they fulfilled certain other requirements in addition to those of age, ambulatory physical condition, history of myocardial infarction at least six months earlier, and absence of diabetes, of syphilis or other serious infections, and of hypertension at the time of the study (one patient had undergone a successful lumbodorsal sympathectomy for previous hypertension). The 100 patients accepted in the study and discussed in these pages are those who met these requirements out of approximately 250 referrals.

At the beginning of the project patients were referred by members of the Advisory Board from their private and clinic practices and from the Out Patient Department of the Massachusetts General Hospital. In all 31 patients (see Table 1) came from the practices of five cardiologists and the hospital files. An additional 12 patients were referred by cardiologists associated with the Cardiac Laboratories of the Massachusetts General Hospital and 1 patient was self referred. After 44 patients had been obtained it was necessary to seek elsewhere for sufficient material. Accordingly cardiologists who had attended graduate and other courses at the Cardiac Laboratories of the Massachusetts General Hospital were circularized. With their aid, 36 patients were obtained (from

TABLE 1-2 Geographical distribution of 100 coronary heart disease patients

<i>Home state</i>	<i>No of patients</i>	<i>Home state</i>	<i>No of patients</i>
Massachusetts	61	Florida	1
New York	8	Alabama	1
New Jersey	5	Ohio	1
Connecticut	4	Illinois	1
Pennsylvania	4	Colorado	1
Maine	3	Kansas	1
Rhode Island	3	Mississippi	1
Texas	2	North Carolina	1
Kentucky	1	South Carolina	1

Texas to Maine) and also entered the hospital for the study. All patients participated in the project without expense to themselves. With the cooperation of Dr. David Littman of the Veterans Administration, an additional 20 patients were obtained from various parts of the country. In this way, no one social, ethnic, or economic group of patients constituted the entire series.

The geographical distribution of patients indicated the same trend toward dispersion of source. While 61 per cent of the patients came from the Commonwealth of Massachusetts (including the Veterans Hospital at West Roxbury and the Murphy Army General Hospital) and 10 per cent more came from three other New England states, the remaining 29 per cent were from the rest of the United States (see Table 2).

Procedure for examination

Patients meeting the requirements were admitted to the Massachusetts General Hospital at the rate of two or three a week for a period of 24 to 72 hours. During this time, the tests, evaluations, and interviews were conducted without haste or pressure in order to allow the patient sufficient recovery time between tests. Since almost all the patients had been hospitalized in the past, the hospital routine was familiar to them. The majority found the tests and interviews interesting and gave wholehearted cooperation, not only during the period of this study but also in the follow-up studies. Two patients whose cooperation was unsatisfactory have shown excessive neurosis and, in the case of one, low grade psychosis.

Upon arrival on the ward floor at 1 P.M., the patient was given a

series of thorough interviews : medical questions stressing health history diet and habits a social interview stressing environment and upbringing an hereditary interview stressing family diseases and ages of death a psychological interview attempting to uncover sources of tension, and a detailed resume of events previous to and during the myocardial infarction The latter material in conjunction with the questionnaires forms the basis for several clinical papers in this series In addition to the direct interviews described a pencil and paper test (the Terman Miles see Chapter VI and Appendix A) and a questionnaire were given to the patient to be filled out during the stay The long interview we found not only served as a method of breaking the ice and obtaining important data but also seemed to improve the patient's emotional status

The patient went to his room at about 4 00 P M to begin the urine collection for the 17 ketosteroid determination In some cases radioactive iodine was administered at this time for the thyroid function test A basal metabolism test was made in the morning and if unsatisfactory for any reason was repeated on a subsequent morning Following breakfast a routine x ray film was taken and fluoroscopy carried out before lunch the electrocardiogram was taken (three standard limb leads three unipolar limb leads and six unipolar precordial leads) Blood smears for a differential count were also taken before lunch

Following the noon meal morphological anthropometric and somatotype studies were made Two hours after lunch the salivary redox test was taken five hours after lunch 25 cc of blood were drawn and held under refrigeration prior to biochemical analysis The patient was then discharged

In addition to the hospital study mentioned here subsequent recalls permitted re examination of about half the patients while repeated serum cholesterol determinations were made in the majority of cases with the cooperation of the patients and their physicians

Selection of Controls

A general group which will be referred to as the unmatched control group of 146 males of age occupation and ethnic origin similar to those of the coronary disease group was employed at the outset of this study However for many purposes it was deemed more satisfactory to adopt the experimentally ideal matched pair

technique as closely as possible since such variables as occupation race and physique might account for some of the differences between patients and unmatched controls * Therefore the matches to the coronary patients were made on an individual basis each matched control resembled some coronary patient in age, height weight body build ethnic origin, and occupation This group of 97 males will be known as the matched control group † The procedure for matching was as follows

1 *Age* The matched control for each patient was rarely more than 3 years older or younger At the most a 5 year difference was allowable if all other criteria were fully satisfied The two groups compared very closely in age the mean difference being 0.7 years

2 *Height* The match was held within 3 cm in the majority of cases the mean difference between the two groups was 2.57 cm

3 *Weight* Matching was done within 4.5 kilos (9.9 pounds) on the average the matched controls (who were taller) were 2.7 kilos (5.9 pounds) heavier, but the ponderal index or height/cube root of weight ratio was the same for the two groups

4 *Body build* This was considered to be very important, and careful matching was done In general the matched control was within a half point of the patient in each component (see Chapter IV for the method of evaluating physique) At no time was there a reversal of dominance as represented by the three components of physique (Sheldon et al. 1940) (a) endomorphy (soft round obese build) (b) mesomorphy (hard, square muscular build), and (c) ectomorphy (fragile thin linear build)

5 *Race* Each match was of the same racial and national origin as was his index patient

6 *Occupation* Since exact matches could not be made for many unusual occupations (leatherette worker for instance), matching was done on the basis of a similar level of physical exertion Hence laborers were paired with laborers professional men with professional men and so on

*For example lipid levels vary not only with the presence or absence of coronary heart disease but also with differences in age and body build and possibly (though not definitely) with race It is therefore possible that variables other than the disease state could result in a difference between coronary disease patients and a general group of unmatched individuals

†Since a group of only 3 women was too small for significant comparison with a group of 97 men no attempt was made to provide matched controls for the women

With six variables to consider in each match the process was a tedious and sometimes difficult one as for example in the finding of a match for a 39 year-old mesomorphic Armenian waiter who came to Boston in 1930

It was not possible to employ the matched pair technique for all studies basal metabolic rate and athletic histories were analyzed for the patients only and a series of unmatched controls was used in evaluating urinary 17 ketosteroids The source of the control group in each instance will be stated in the text

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CHAPTER II

Clinical Appraisal of the Coronary Group

It is the purpose of this chapter to describe the 100 coronary heart disease patients studied with respect to certain variables such as sex age occupation and so on to analyze the character and mode of onset of both the premonitory symptoms and the acute prodromal symptoms and to describe the clinical findings at the initial examinations in 1949

Composition of the Group

Sex

Of the 100 patients examined 97 were men and 3 were women These proportions are almost the same as had been reported previously by Glendy Levine and White (1937) in a group of 100 persons who had experienced myocardial infarction prior to the age of 40 they found the ratio of men to women to be 96 to 4 Discussion of the relation of masculinity to coronary heart disease will be reserved for Chapter VI

Age

In the present study the 3 women examined were 35, 39, and 40 years of age The ages of the 97 men at the time of the acute episodes ranged from 22 to 40 years averaging 35.4 There were 8 men between 20 and 29 years 28 men between 30 and 34 years and 61 men between 35 and 40 years The age at the time of examination ranged from 24 to 51 years with an average of 38.2 The lapse of time between onset of myocardial infarction and our examination is given in Table 1

Race

The question of racial predisposition to coronary heart disease is far from being answered The selection of patients for study the

TABLE II-1 Lapse of time between onset of myocardial infarction and our initial examination of 97 male patients

<i>Years</i>	<i>No of patients</i>	<i>Years</i>	<i>No of patients</i>
0.5 - 1.0	17	5.51- 6.0	3
1.01- 1.5	14	6.01- 6.5	3
1.51- 2.0	15	6.51- 7.0	3
2.01- 2.5	8	7.01- 7.5	4
2.51- 3.0	8	7.51- 8.0	2
3.01- 3.5	2	8.01- 9.0	3
3.51- 4.0	4	9.01-10.0	2
4.01- 4.5	3	10.01-11.0	0
4.51- 5.0	4	11.01-12.0	1
5.01- 5.5	0	26.01-27.0	1

This man was examined by Dr H B Sprague in 1923

origin of the various reports and the interpretation of the final results all complicate the issue. These questions and other problems concerning race in relation to coronary heart disease are more fully discussed in Chapter III.

Nearly all the ethnic groups present on the east coast (the home of 70 per cent of the patients) were represented in this series (see Chapter III Table 6). The progenitors, either male or female of nearly half the group originated in the British Isles. Individuals of Mediterranean or Eastern Mediterranean origin comprised 37 per cent of the entire group, a proportion well in excess of their representation in the areas from which the sample was drawn (Hooton 1950).

Occupation

Several reports in the literature have been concerned with unravelling evidence of a causal relationship between coronary heart disease and occupational pursuits (Yater et al 1948, Gordon et al 1939). This question is considered in greater detail in Chapter V. Suffice it to say at this juncture that it is evident from this study that there are excessive numbers of patients in certain occupational categories: the managerial comprises 42 per cent, the semiprofessional 7 per cent, professional (including doctors) 11 per cent, semiskilled labor 30 per cent, skilled 4 per cent, and unskilled 3 per cent. Thus in this limited series, as in other more extensive series, certain types of occupation are found to pre dominate.

TABLE II-2 Distribution by month of acute episodes of myocardial infarction in 100 patients (97 male and 3 female)

<i>Month</i>	<i>No of patients</i>
January	13
February	4
March	11
April	5
May	13
June	1
July	7
August	4
September	10
October	11
November	12
December	11

Incidence and Symptoms

Incidence of infarction

The distribution of cases by month is shown in Table 2. The onset of acute episodes of coronary heart disease in our patients during the fall and winter months showed a greater absolute incidence which on statistical analysis is significant.

The series of patients studied however, is too small to warrant the drawing of definite conclusions concerning the relation of weather to coronary episodes.

As can be seen from Table 3 which gives the distribution of the acute episodes by time of day the majority occurred during the hours of increased activity with the greatest incidence in the early afternoon. There appeared to be a decline in the rate of occurrence of myocardial infarction between the hours of 3 P M and 6 A M.

TABLE II-3 Incidence of myocardial infarction by time of day in 100 patients (97 male and 3 female)

<i>Time</i>	<i>No of patients</i>	<i>Time</i>	<i>No of patients</i>
A M midnight-3	8	P M noon-3	27
3-6	5	3-6	10
6-9	17	6-9	11
9-noon	12	9-midnight	10

TABLE II-4 Symptoms preceding myocardial infarction in 64 male patients*

<i>Symptom</i>	<i>No of patients</i>
Angina pectoris	41
on effort	32
on emotional strain	5
after heavy meals	2
at rest	1
Pain radiating from chest	15
to arms	14
to shoulders	1
Dyspnea on exertion	22
Fatigue	7
Indigestion (upper abdominal distress)	20
after exercise	9
after eating	8
on emotional strain	3
Nervousness (tachycardia or palpitation)	4

36 patients (33 male and 3 female) had no symptoms prior to the acute episode

Symptoms

Of the 64 patients who gave a history of their symptoms preceding the acute episode (see Table 4) 8 said that the complaints had been present for longer than one year. Of these 8 patients 3 gave indigestion as a symptom, 2 nervousness and 3 angina pectoris. Three others had complained of indigestion and nervousness for as long as four years. 1 reported dyspnea for as long as five years. The 52 remaining patients had noted some form of distress (angina pectoris in 38 cases) for less than one year, in most cases for only a few months. Three of the 38 who had had angina pectoris for less than a year had suffered tightness in the chest on exertion for only three days before the acute attack. Symptoms which may represent a partial occlusion of one of the coronary vessels progressing with continued activity to complete occlusion and infarction.

It is noteworthy that only 4 of the 100 patients suffered no pain during the attack, although they did have other complaints such as dizziness, nausea and vomiting and so on (see Table 5). The pain when experienced lasted on the average, approximately six hours with extreme variations of from twenty minutes to seventy two hours.

TABLE II-5 Symptoms at onset of acute episode of coronary heart disease for 100 patients (97 male and 3 female)

<i>Symptom</i>	<i>No of patients</i>
Chest pain (substernal and/or precordial)	96
Nausea	15
Indigestion	14
Dyspnea	10
Vomiting	8
Excessive sweating	8
Dizziness	5
Weakness	2
Cyanosis	2
Headache	1
Palpitation	1
Choking	1

The locations to which the chest pain radiated were not always the classical sites in less than half of the instances of radiated chest pain (29 out of 68 patients) did the pain radiate down both arms. It is noteworthy that in 28 cases there was chest pain with no radiation. These observations are summarized in Table 6.

TABLE II-6 Radiation of pain during acute episode of coronary heart disease for 96 male patients*

<i>Pain</i>	<i>No of patients</i>
Radiation of pain to	68
both arms	29
left arm	17
left wrist and hand	11
left hand and fingers	9
middle of back	8
left shoulder	5
left elbow	4
upper abdomen	4
mandible and teeth	3
throat	2
right shoulder	2
right arm only	1
both clavicles	1
left ear	1
single radiation	39
multiple radiation (combinations of above)	29
No radiation of pain	28

4 patients (1 male and 3 female) did not experience pain

TABLE II-7 Activity at onset of acute episode of coronary heart disease for 100 patients (97 male and 3 female)

<i>Activity</i>	<i>No of patients</i>
Resting	22
Walking	21
Manual labor	18
Sleeping	11
Performance of professional duties	8
Exercising (calisthenics baseball)	6
Climbing steps	4
Driving or riding	3
Getting out of bed	3
Eating	2
Running	1
Dressing	1

Activity at onset of acute episode

The types of activity in which the individuals were engaged immediately prior to the acute episode are summarized in Table 7

Of the 18 patients listed as having their major attack while performing manual labor 9 experienced it while engaged in some type of work to which they were not accustomed. In 2 of these cases unusual excitement superimposed on the unusual activity was perhaps an additional factor. A total of 21 were engaged in some type of activity exercise or otherwise that required greater work on the part of the heart than was required by their usual daily routine. It is believed that this may have been a factor in the development of infarction of the myocardium at least in some patients. Of the 100 cases one third were resting or sleeping at the onset of the acute myocardial infarction.

Status and Clinical Findings at Initial Examination

Seventy of the patients had been hospitalized at the time of the acute myocardial infarction for an average of 6.2 weeks and had remained inactive following the hospitalization period for an average of three months. Twenty-one patients had been treated at home for a similar period and 9 cases had gone unrecognized or ignored during the illness. No attempt was made in this study to evaluate the methods of treatment that had been carried out during the acute illness.

In the majority of cases the physical examination made for

the present study was remarkably unrevealing. This observation is not new. It is the experience of most physicians who have the opportunity to see cases of coronary heart disease after the initial acute episode.

It was striking to observe in this group that the features of almost every individual appeared to be at least a decade older than his chronological age. This raised the question that has been considered by Carrell and others. How does the rate of living affect the longevity of the individual? The typical physique of coronary heart disease patients (discussed in Chapter IV) is associated with an energy expenditure that can be far greater than the expenditure of those with a more linear physique who do not usually experience the disease. Are persons who experience coronary heart disease at a relatively young chronological age therefore, actually a decade older by physiological standards? This hypothesis has been suggested by Paul D. White and Samuel A. Levine in their various publications and lectures.

Heart

In only 1 case was a murmur grade 3 apical systolic, considered of any consequence although a grade 1 apical systolic murmur was recorded in 7 other cases. In all 8 cases the murmurs were found in hearts reported to be enlarged in the left ventricular component. The aortic second sound was greater than the pulmonic second sound in 74 cases and P2 was greater than or equal to A2 in the remaining 26 cases.

Abnormal jugular pulsations were found in 1 case accompanied by tachycardia and by gallop rhythm which was also heard in 3 other cases.

Blood pressure

The highest systolic pressure recorded was 160 mm. of mercury the highest diastolic pressure was 108 mm. of mercury. The average blood pressure for the entire group was 123 systolic and 81 diastolic. The systolic and diastolic pressures exceeded 150 and 100 mm. of mercury respectively in only 5 instances. However only 1 patient could be classified as having hypertensive heart disease (at the time of examination his pressure was normal owing to a sympathectomy). It will be recalled that one of the criteria of selection



FIGURE 11-1 X ray picture showing an aneurysm of the left ventricle apical portion

of patients for this study was the absence of hypertension. This fact helps to explain the blood pressure findings.

Fluoroscopic and x ray findings

During our initial examination 97 of the patients were studied by x ray consisting of both fluoroscopy and 7 foot chest films in the P-A view. In addition left and right oblique views were taken in 10 cases. In 39 instances the heart was enlarged as reported by the roentgenologists. Even though the cardiothoracic ratio is an inaccurate means of determining the relative size of the heart this was computed in each case and in 22 instances the heart was found to be 50 per cent or more of the transverse diameter of the inner rib cage.

Two cases were found of left ventricular aneurysm with paradoxical pulsations. In 1 of these cases (see Figure 1) the infarction had occurred nine years previously in the other case only one year before. Eight cases presented fluoroscopic evidence of diminished pulsations along the lateral margin of the left ventricle which the roentgenologists interpreted as being possible old areas of infarction with scarring. This incidence is much lower than that reported by other authors (Dack et al.)

Electrocardiographic findings

Using the three standard limb leads three unipolar limb leads (aVR, aVL, aVF) and six unipolar precordial leads (V1 to V6) evidence of infarction was demonstrable in every case including one of ten years duration and another of twenty one years duration. This 100 per cent electrocardiographic confirmation is not surprising because in this study only those cases were selected which had an absolutely certain diagnosis. There were 54 cases of anterior or anteroapical infarction as evidenced by QRS wave, ST segment and T wave changes in standard limb leads 1 and/or 2, aVL and the precordial leads. There were 40 cases of posterior or posterolateral infarctions as shown by alterations of QRS, ST, T complexes in standard limb leads 2 and/or 3 and lead aVF. In the majority of individuals examined the septum was involved to some extent. Six cases presented the electrocardiographic picture of both anterior and posterior infarctions. The results are summarized in Table 8.

TABLE II 8 Electrocardiographic findings in 100 patients (97 male and 3 female)

	<i>No of patients</i>
Distribution of myocardial infarction	
anterior or anteroapical site of infarction	54
posterior or posterolateral site	40
both sites	■
Disturbances of rhythm	
normal sinus rhythm	93
sinus tachycardia	3
sinus bradycardia	3
premature contractions (auricular)	1
paroxysmal tachycardia	0
auricular fibrillation or flutter	0
Conduction defects	
A V block—partial	2
A V block—complete	0
right bundle branch block	3
left bundle branch block	2
other impaired intraventricular conduction	■
no conduction defects	91
Axis deviation	
left ventricular hypertrophy	11
left axis deviation	14
right ventricular hypertrophy	0
right axis deviation	3
no axis deviation	72

Miscellaneous findings

ARCUS SENILIS Arcus senilis has been considered to be related to cholesterol metabolism, and it was stated by Boas (1945) that the incidence of arcus senilis increases with hypercholesterolemia. This concept was later questioned and additional evidence was presented which did not support Boas' thesis (Garn and Gertler 1950). In the present study only 5 patients had an arcus senilis. The level of total cholesterol in their serum averaged 275 mg per cent.

TOBACCO AND ALCOHOL The question of the effects of tobacco and alcohol on coronary heart disease and the possible relation between these two factors was considered in this study. The results are summarized in Tables 9 through 12.

It is evident that the coronary heart disease group smoked a few more cigarettes per day than did the unmatched control group. These data, however, do not give any information on the effect of smoking on the cardiovascular system such as has been presented by several authors (Levy et al 1947; Evans and Stewart 1943).

TABLE II-9 Daily tobacco use in coronary heart disease group of 90 males* and unmatched control group of 139 males† (Mean \pm S E)

	<i>Cigarettes smoked</i>	<i>Cigs smoked</i>	<i>Pipeful‡ smoked</i>
Coronary group	19.4 \pm 1.6	17 \pm 10	11 \pm 29
Control group	13.8 \pm 1.1	25 \pm 09	56 \pm 16

* 7 patients did not respond to the questionnaire

† 7 controls did not respond to the questionnaire

‡ Each pipeful was considered to be 0.1 ounce

TABLE II-10 Smokers and non smokers in coronary heart disease group of 90 males* and unmatched control group of 139 males†

	<u>SMOKERS</u>		<u>NON SMOKERS</u>	
	<i>No</i>	<i>%</i>	<i>No</i>	<i>%</i>
Coronary group	81	90	9	10
Control group	107	77	32	23

* 7 patients did not respond to the questionnaire

† 7 controls did not respond to the questionnaire

TABLE II-11 Weekly alcoholic consumption in coronary heart disease group of 92 males* and unmatched control group of 140 males† (Mean \pm S E in ounces)

	<i>Beer</i>	<i>Wine</i>	<i>L. quort‡</i>	<i>Total</i>
Coronary group	25 \pm 4.87	2.9 \pm 1.14	6.4 \pm 1.27	34.3
Control group	32 \pm 5.08	2.5 \pm 0.56	3.6 \pm 0.69	38.1

* 5 patients did not respond to the questionnaire

† 6 controls did not respond to the questionnaire

‡ Rye and scotch whiskey and gin

TABLE II-12 Consumers of alcohol in coronary heart disease group of 92 males* and unmatched control group of 140 males†

	<u>CONSUMERS</u>		<u>ABSTAINERS</u>	
	<i>No</i>	<i>%</i>	<i>No</i>	<i>%</i>
Coronary group	69	75	23	25
Control group	111	79	29	21

* 5 patients did not respond to the questionnaire

† 6 controls did not respond to the questionnaire

English et al, 1940) It should not be inferred from these results that cessation of smoking will necessarily benefit or prevent coronary heart disease

In Table 10 the smokers and non smokers in the unmatched control group and coronary heart disease group are considered Although it is evident not only that (a) the smokers in the coronary group smoked somewhat more than the smokers in the control group but that (b) there were proportionately more in the coronary disease group who smoked the difference seems to be unimportant

In Tables 11 and 12 two topics are considered (a) the amount of alcoholic beverage consumed by the two groups and (b) the number in each group who abstained from alcoholic beverages In Table 11 it will be seen that the coronary heart disease group ingested more liquor in the form of whiskey and gin But in total quantities the unmatched control group ingested more alcoholic beverages of all kinds i.e. 38 ounces to 34 ounces

In Table 12 it is evident that the difference between abstainers in both groups was insignificant

From this study no definite conclusions may be drawn as to the effects of alcohol on the development of atherosclerosis or on the precipitation of a myocardial infarction

BLOOD GROUPS Boyd (1950) has applied a genetic system of classification to man He bases his method on the hypothesis that the genes which determine blood groups do not differ fundamentally from the genes which affect morphological characteristics Such a system is necessarily limited by our understanding of the complex biochemical factors involved but it has nevertheless been established on a firm footing by Boyd Extending Wiener's proposal (1951) of racial classification by means of blood groups Boyd (1950) has suggested six racial divisions based on blood group differences

Since the refinements of Boyd's technique were unavailable in this study our data on blood groups and Rh factors cannot be employed with as great assurance as Boyd's data Nevertheless certain differences did exist even in this rough classification The control group had a larger percentage of Group O and of Group O with Rh positive than did the coronary heart disease group but a smaller percentage of Group A and Group A with Rh positive (see Table 13)

TABLE II-13 Blood groups · Rh factors and combinations thereof in coronary heart disease group of 94 males* and unmatched control group of 145 males†

	CORONARY PATIENTS		UNMATCHED CONTROLS	
	No	%	No	%
Blood group				
A	37	46.0	51	35.2
B	14	17.2	21	14.4
AB	4	4.9	4	2.8
O	26	32.2	69	47.5
Rh factor				
positive	71	88.8	116	80.0
negative	9	11.2	29	20.0
Blood group and Rh				
A+	27	40.3	38	26.1
A—	4	5.9	13	8.7
B+	10	14.9	17	11.7
B—	0	0.0	4	2.7
AB+	3	4.5	3	2.1
AB—	1	1.4	1	.7
O+	19	28.3	58	40.5
O—	3	4.5	11	7.6

For 3 of the 97 male coronary heart disease patients neither blood group nor Rh factor was recorded. In the remaining group of 94 patients the blood group was not recorded in 13 cases and the Rh factor was not recorded in 14 other cases.

†For 1 of the unmatched controls no data were recorded.

Prognosis

At the time when this report was undertaken (December 1 1949) 10 patients in this series had died since examination all apparently from recurrent infarctions. 6 of these deaths occurred after one additional infarction, 3 after two additional infarctions and 1 after three additional infarctions. Twenty six others had suffered additional infarctions including 2 who had had a total of three infarctions and 1 a physician who had had a total of four infarctions but who still carried on a limited practice.

Eighteen of the patients had not restricted their work or activity in any way and had no complaints referable to the cardiovascular system at that time. Twenty four had voluntarily limited their work or exercise and likewise had no cardiovascular complaints. One man was crippled by gout. The remaining 57 patients had complaints of angina of effort, dyspnea or a combination of complaints (see Table 14). Two were listed as heavy users of nitroglycerine, 1 taking approximately 300 tablets per week.

The 90 living patients had survived an average of 3.92 years.

TABLE II-14 Symptoms in 1949 of the 90 living patients with previous myocardial infarction

<i>Symptoms</i>	<i>No of patients</i>
Angina pe toris	36
Dyspnea	16
Palpitation	9
Fatigue	4
Dizziness	2
Crippled by gout	1
Limitation of activity without specific complaints	24
No complaints	18

from the date of the acute episode until this report. One man was alive 22.5 years after the original episode though crippled by gout at this time. The 10 patients who had died since our original examination had survived an average of 3.5 years including 1 who had remained alive and active for over 11 years. Eight of the 10 who died had had preceding complaints for from two months to as long as five years consisting of mild to severe dyspnea and angina pectoris associated principally with effort. Thirty-six patients who had complaints before infarction such as angina pectoris, dyspnea or palpitation continued to have these same complaints frequently to a more severe degree afterwards.

There were 16 who listed some complaints before infarction who at the time of writing were free of symptoms. However it must be remembered that the majority of these patients had markedly curtailed their activities and did not extend themselves to the point of inducing angina pectoris, dyspnea or other symptoms.

Summary

The findings discussed in this chapter leave little doubt that pure coronary heart disease (that is uncomplicated by hypertension, xanthomatosis, diabetes or nephrosis) is predominantly a male disease prior to the age of 40. The patients in this study in all instances revealed prodromal symptoms varying from direct cardiac symptoms such as chest pain (both precordial and sub-sternal) to seemingly unrelated symptoms such as indigestion or headache. However it is noteworthy that in 96 per cent of the patients the symptoms were referable to chest pain. There appeared to be a relation between season of the year and infarction, for 60

per cent of the acute episodes occurred during a 5 month period between November 1 and March 30. The use of alcohol and of tobacco was greater in the coronary heart disease group but the differences were not sufficient to imply a causal relation.

The 97 men in the coronary group appeared about a decade older than their chronological stated age. Aside from this clinical observation there were no other striking clinical phenomena. Only 2 instances of left ventricular aneurysm and only 10 instances of diminished or paradoxical pulsation were observed during fluoroscopic examination. The heart sounds and the electrocardiograms did not reveal any unusual or definitive diagnostic features. Blood studies either by groups or Rh factors did not reveal any suggestive clues as to genotypes or phenotypes in coronary heart disease.

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CHAPTER III

Family Incidence The Role of Heredity and Race

IN clinical practice coronary heart disease is not infrequently encountered in siblings and cardiologists who have been established for some years often have treated both father and son. Such observations have led to the conclusion that coronary heart disease is a familial disease that it runs in families. Some fairly impressive material has been published to support this contention (Musser and Barton 1931 Gates 1946).

It has also been observed that patients with coronary heart disease often come from short lived families from families showing other cardiovascular disorders or from families with diabetes renal disease and/or other degenerative diseases. These observations would suggest in turn either that the life span of the parents of the patients was shortened by coronary heart disease (though not necessarily diagnosed as such) or that the factors for the development of the disease were pleiotropic in character and diseases of the coronary arteries were one expression of the general syndrome.

Clinicians have also noted that in this country Jews seemingly have a high while Negroes have the lowest incidence of coronary heart disease (Yater et al 1948). Such observations together with tentative reports from other countries suggest that there is a racial factor involved.

When these observations are taken together—the facts that the disease appears to be familial that it is associated with a shortened life span in the parents of patients and that there appear to be racial variations in the incidence of the disease—it is reasonable to suspect the existence of hereditary genetic factors in the etiology of coronary heart disease. This being so the next step is to attempt to uncover these factors.

TABLE III-1 Survival of parents of coronary heart disease group of 97 males and unmatched control group of 146 males

	PARENTS OF CORONARY GROUP		PARENTS OF CONTROL GROUP	
	No	%	No	%
Mothers	97	100	146	100
living	56	58	107	73
dead	41	42	39	27
Fathers	97	100	146	100
living	32	32	65	45
unknown	3	4	5	3
dead	62	64	76	52
Total parents	194	100	292	100
living	88	45	173	59
unknown	3	2	5	1
dead	103	53	114	39

Family Mortality and Average Length of Life

Method

During the course of the interviews both the patients and the 146 controls were questioned about the physical condition of their parents grandparents and siblings whether they were living and if not the cause of death (if known) The data obtained from these interviews (see Appendix B) were compared with those obtained from detailed written questionnaires filled out by each individual subsequent to the interview thus duplicate records were obtained for both the patients and the controls Discrepancies between the two records were resolved by further communication with the subjects or with referring physicians or by recourse to hospital records or to relatives of the patients In cases of doubtful information or questionable reports no entries were made

From the final records master genealogical charts were drawn up for both groups (see Appendix C) and from these master charts the final tabulations were computed It should be noted that these tabulations represent the situation at the time of the final interview

Frequency and cause of death among parents

Table 1 gives the number and proportion of parents who were living or dead at the time of the final interview It shows that the proportion of parents living at the time of the final interview was higher in the unmatched control group than in the patient group

TABLE III-2 Mean age of parents at time of death * unmatched control group and coronary heart disease group

	PARENTS OF CORONARY GROUP		PARENTS OF CONTROL GROUP		Difference years
	No	Age in years	No	Age in years	
Mothers	39†	55.6 ± 2.08	35‡	59.0 ± 2.10	4.4
Fathers	61§	58.8 ± 1.54	72	59.7 ± 1.60	0.9
Difference		3.2		0.7	

*For a total of 11 parents the age at death was not known hence the totals are smaller than in Table 1

†2 mothers ages at death were unknown

‡4 mothers ages at death were unknown

§1 father's age at death was unknown.

||4 fathers ages at death were unknown

Of the mothers of 146 controls 73 per cent were alive as compared with 58 per cent of the patients mothers. Similarly 45 per cent of the fathers of the controls were alive as compared with 32 per cent of the fathers of the patients. For total parents 59 per cent of the parents of the controls were alive as compared with 45 per cent of the parents of the patients. Since these differences are statistically significant it is concluded that mortality is higher among the parents of the 97 male patients.

In order to determine whether the difference in mortality could be attributed to a difference in the age distribution of the two groups of parents the ages of the surviving parents at the time of the final interview were compared. The surviving mothers of the control group and patient group respectively averaged 63.9 years and 64.4 years; the fathers averaged 66.4 years and 66.0 years. The slight differences of .5 year and .4 year were too small to be significant. Hence the different mortality cannot be attributed to an age difference.

The average ages at death of mothers and fathers of the coronary heart disease patients and the controls are compared in Table 2. It will be noted that the averages for the coronary heart disease group were in each case somewhat less than for the control group. This might have been anticipated in view of the higher percentage of dead parents in the coronary heart disease group (see Table 1). However, this difference in the average age at death of the parents in both groups is not statistically significant. It will also be noted that the average age at death of the mothers was somewhat less (although not significantly) than that of the fathers in both groups.

This is in keeping with statements by Eppinger and Levine (1934) who suggested that the parents of patients with angina pectoris show a somewhat lower mean age at death than the general population and that the patients' mothers die at an earlier age than their fathers.

Since a higher proportion of the patients than of the controls' parents were deceased it was of interest to compare the causes of death. As shown in Table 3 the deceased parents of the patients showed a higher percentage of deaths attributable to disease of the cardiovascular system and fewer deaths attributable to certain other causes.

Of the deceased mothers 51.3 per cent in the patient group died of cardiovascular disorders of all kinds as compared with 35.9 per cent in the control group. Of the deceased fathers 64.6 per cent in the patient group died of cardiovascular defects of all kinds as compared with 46.2 per cent in the control group.

The patients' fathers showed a larger proportion of deaths due to disease of the coronary arteries 37.1 per cent of those deceased as compared with 18.5 per cent of deceased fathers of the control group. The difference is significant. There was practically no difference in the percentage of deaths from disease of the coronary arteries among the mothers of the two groups 9.8 per cent in the coronary group and 7.7 in the control group.

Naturally certain questions arise as to the validity of these findings. While the results given here are derived at first hand from personal interviews and questionnaires all the information stems from the same source and is subject to bias or error by the individual. It is quite possible that a patient might give retrospective diagnosis—that is, assume that the parent necessarily died of the disorder that is a source of concern to the patient himself. However, it should be pointed out that the proportions of deaths said to be due to old age, unknown causes, accident, and so forth are comparable in the two groups.

Bearing these cautions in mind the data suggest then that the parents of coronary disease patients show a high proportion of deaths due to disorders of the heart and circulation and that much or all of the excess may be due to diseases of the coronary arteries. While this in itself does not confirm the factor of inheritance it is extremely suggestive.

TABLE III-3 Cause of death for parents and siblings of coronary heart disease group of 97 males and unmatched control group of 146 males

Cause of death	CORONARY GROUP						CONTROL GROUP					
	Mother			Father			Siblings			Mother		
	No	%	No	No	%	No	No	%	No	No	%	No
Diseases of the coronary arteries	4	9.8	23	37.1	5	8.6	3	7.7	14	18.5	1	1.0
Other cardiovascular diseases	17	41.5	17	27.5	11	19.0	11	28.2	21	27.7	7	7.2
Total cardiovascular diseases	21	51.3	40	64.6	16	27.6	14	35.9	35	46.2	8	8.2
Cancer and other neoplasms	5	12.2	3	4.8	2	3.4	5	12.8	7	9.2	4	4.1
Diabetes mellitus	1	2.4	1	1.6	2	3.4	1	2.6	2	2.6	1	1.0
Renal diseases	1	2.4	1	1.6			2	5.1	3	3.9	2	2.0
Anemia (pernicious)									1	1.3		
Liver diseases							1	2.6				
Diseases of infancy (various)					15	25.9					44	44.9
Influenza and pneumonia	5	12.2	8	12.9	3	5.2	4	10.3	6	7.9	2	2.0
Tuberculosis (all forms)					5	8.6	2	5.1	5	6.6	3	3.1
Infections (scarlet fever diphtheria mastoiditis meningitis)	1	2.4			5	8.6	3	7.7	1	1.3	6	6.1
Syphilis			1	1.6								
Alcoholism												
Neurological (epilepsy paralysis agtans)			1	1.6	2	3.4			1	1.3		
Violence and accident	2	4.9	4	6.5	6	10.4	2	5.1	6	7.9	16	16.3
Miscellaneous and unknown	5	12.2	3	4.3	3	3.4	5	12.8	8	10.5	12	12.2
TOTAL	41		62		58		39		76		98	

Sex ratios among siblings

Since some disorders are characterized by a disproportionate sex ratio apparently due to factors that act as lethal in one sex and as semilethal in the other it was of interest to study the sex ratios of the siblings. These were calculated for all 100* patients and the 146 male controls. The young coronary patients had 388 siblings (not counting those stillborn whose sex is unknown). Of this 388 total 53 per cent were males. In the control group there were 482 siblings of whom 246 or 51 per cent were males. The ratio of males to females does not depart significantly from the theoretical 1.06:1 nor do the ratios in the two groups differ significantly. From the total number of siblings it was calculated that the average numbers of children in a patient's and in a control's family were 4.88 and 4.30 respectively.

Although the patients and controls may not yet be considered to have completed their own families the average numbers of offspring at the time of the final interview were 1.77 and 1.70 respectively. The ratios of male to female children were 0.85:1.0 and 1.03:1.0. It is obvious that these differences are not significant.

Frequency and cause of death among siblings

Since the parents of the patients showed a higher mortality and a larger proportion of deaths attributable to the heart and vascular system it was of interest to compare the siblings of the patients and the controls in this respect. Of the 482 siblings of the 146 control subjects 98 or 20 per cent had died up to the time of the interviews. Of the 388 siblings of the 100 patients 58 or 15 per cent had died up to the time of the interview. The difference in mortality is not significant.

The causes of death however show a marked difference between the two groups. As shown in Table 3 the deceased siblings of the coronary patients showed an excess of cardiovascular disorders. Of the 58 deceased siblings of the young coronary patients 27.6 per cent died of various cardiovascular disorders as contrasted with 8.2 per cent of the deceased siblings of the control group; this difference in percentage is significant. Much of the difference is due to the higher coronary heart disease rate among the siblings.

Since the results are not affected by the sex of the proband (or index patient) it was allowable to include both the 97 males and the 3 females in this tabulation.

TABLE M-3 Cause of death for parents and siblings of coronary heart disease group of 97 males and unmatched control group of 146 males

Cause of death	CORONARY GROUP						CONTROL GROUP					
	Mother			Father			Mother			Father		
	Siblings			Siblings			Siblings			Siblings		
	No	%	No	No	%	No	No	%	No	No	%	No
Diseases of the coronary arteries	4	98	23	37.1	5	8.6	3	7.7	14	18.5	1	1.0
Other cardiovascular diseases	17	41.5	17	27.5	11	19.0	11	28.2	21	27.7	7	7.2
Total cardiovascular diseases	21	51.3	40	64.6	16	27.6	14	35.9	35	46.2	8	8.2
Cancer and other neoplasms	5	12.2	3	4.8	2	3.4	5	12.8	7	9.2	4	4.1
Diabetes mellitus	1	2.4	1	1.6	2	3.4	1	2.6	1	2.6	1	1.0
Renal diseases	1	2.4	1	1.6			2	5.1	3	3.9	2	2.0
Anemia (pernicious)									1	1.3		
Liver diseases							1	2.6				
Diseases of infancy (various)					15	25.9					44	44.9
Influenza and pneumonia	5	12.2	8	12.9	3	5.2	4	10.3	6	7.9	2	2.0
Tuberculosis (all forms)					5	8.6	2	5.1	5	6.6	3	3.1
Infections (scarlet fever diphtheria mastoiditis meningitis)	1	2.4			5	8.6	3	7.7	1	1.3	6	6.1
Syphilis			1	1.6								
Alcoholism									1	1.3		
Neurological (epilepsy paralysis agtans)			1	1.6	2	3.4			1	1.3		
Violence and accident	2	4.9	4	6.5	6	10.4	2	5.1	6	7.9	16	16.3
Miscellaneous and unknown	5	12.2	3	4.3	2	3.4	5	12.8	8	10.5	12	12.2
TOTAL	41		62		58		39		76		98	

TABLE III-4 Frequency of coronary heart disease in parents of coronary heart disease group of 100 (97 males and 3 females) and of unmatched control group of 146 males

	CORONARY GROUP		CONTROL GROUP	
	No of parents	% of 100 total parents	No of parents	% of 29 total parents
Father only	23		14	
Mother only	1		3	
Both parents	6*		0	
TOTAL	30	15.0	17	5.8

*3 pairs of parents

As described in the previous sections the genealogies which are given individually in Appendix C were analyzed in order to determine whether the mode of inheritance followed any simple genetic model. The genealogies for the 146 control subjects are also included since they serve as an indication of the frequency of coronary heart disease in the parents of individuals of comparable age who were at the time of examination free from coronary heart disease. The findings are tabulated in Table 4. The genealogies may be less than conclusive because the life experience with respect to coronary heart disease is not yet complete.

In 73 of the 100 coronary heart disease cases *neither* parent exhibited the disease so far as is known. In only 3 cases did *both* parents have the disease. These 3 mothers plus 1 other whose husband did not have the disease were the only 4 mothers said to have had it whereas a total of 26 of the fathers were said to have suffered from it.

Five out of 58 or 8.6 per cent of the siblings of the coronary patients experienced coronary heart disease whereas only 1 out of 98 or 1 per cent of the siblings of the unmatched controls had coronary heart disease. The difference is statistically significant.

For 131 of the 146 controls *neither* parent was said to have had coronary heart disease. In no case were *both* parents of controls affected. There were 3 mothers with a history of the disease—almost the same number as in the patient group. Only 14 fathers were affected however compared with 26 fathers of patients.

The incidence of the disease then is significantly greater in the parents of our patients (15.0 per cent) than in the parents of controls (5.8 per cent).

The proportion of males to females among the parents who

had had coronary heart disease varied in the two groups for the patients parents it was 26.4, or 65.1 and for the controls parents it was 4.7. The difference between these two ratios is large but in view of the small numbers of parents affected it is not statistically significant. The larger number of males in both ratios is in keeping with the general observation that this is a predominantly male disease.

The genealogies are interesting in that they fail to show a spectacular number of family members with coronary heart disease. While Herapath and Perry (1930), Coombs (1930) and Boissevain (1931) have all described families with one affected parent and many affected siblings such family lines are probably exceptional cases and may be due to chance.* In the present study even though all the family lines in the patient group were selected on the basis of one or more affected individuals few genealogies replete with coronary heart disease are found.† The genealogy of Patient No. 18 (Appendix C) shows 7 siblings, 5 male and 2 female of whom 3 males were affected. The father was also affected. The genealogy of Patient No. 26 shows an affected mother and 2 affected siblings out of 4. But genealogies with many affected siblings are absent, though this may well be attributable in part to the relatively low age of the group. Similarly the control series fails to evidence family lines of the type described by Boissevain (1931) and by others.

From the data it would appear to be highly unlikely that the disorder is inherited either as a simple Mendelian dominant or as a dominant covert in the female. The proportion of affected fathers of patients (26 out of 100 fathers) is too small to fit either mode of inheritance.‡

The possibility that the disorder was inherited as a Mendelian recessive was checked further by examining the 3 cases in which both parents were affected. If the disease was so inherited then both parents would be homozygous for the disorder and all the offspring would be affected. But in these 3 cases among 20 siblings of affected patients there were no clear cases of coronary heart

*See Allan (1933).

†Coronary heart disease was a relatively rare diagnosis forty years ago and was doubtless often missed.

‡If it were either a sex influenced, a sex limited or a simple dominant inheritance approximately 50 per cent of the fathers would be expected to show the disease assuming high penetrance.

disease. It is therefore highly unlikely that the disorder is inherited as a simple Mendelian recessive.

The evidence is thus against the possibility of a simple mode of inheritance for coronary heart disease either as a dominant or as a recessive even considering its masked nature in the female. However the data do suggest that the disease is familial (as witness the higher incidence of the disease in the parents and siblings of the patients). The most definite statement that can be made is that the disorder runs in families possibly a multiple factor condition with at least one dominant factor.

Findings on Race

The statement has often been made that coronary heart disease has an unusually high incidence in one racially distinct group or an unusually low incidence in another. With this in mind the ethnic origins of each coronary patient were analyzed in detail including the nationality of both parents (see categories in Table 5) and their place of birth as well as his own.

TABLE III-5 Nationality categories of coronary heart disease group*

Group	Symbol	Description
1 Old American	A	Primarily northwestern European mixture resident in the North American continent for three or more generations (Hrdlicka 1925)
2 Austrian	An	
3 Armenian	Ar	
4 Belgian	Be	
5 British Isles	B	A mixture of English Scotch Irish.
6 Danish	D	
7 English	E	Primarily second and third generation English
8 French	F	
9 French Canadian	FC	
10 German	G	
11 Irish	I	Primarily second and third generation Irish.
12 Italian	I	
13 Jewish	J	Primarily a blend of eastern Mediterranean racial elements forming an endogamous group (Coon 1939)
14 Portuguese	P	
15 Negro	N	Primarily a Gold Coast-Slave Coast blend usually with Groups 1 and 5
16 Syrian	S	

*There were no individuals of "pure" Scotch, Welsh, Swedish, or Chinese origin, or of other nationalities not included in the table.

TABLE III-6 Nationality of parents of coronary heart disease group of 100 (97

PATER- NAL NATIONALITY	MATERNAL NATIONALITY						
	<i>Old American (A)</i>	<i>Austrian (Au)</i>	<i>Armenian (Ar)</i>	<i>Belgian (Be)</i>	<i>British Isles (B)</i>	<i>Danish (D)</i>	<i>English (E)</i>
Old American (A)	15				1		
Austrian (Au)		1					
Armenian (Ar)			1				
Belgian (Be)				1			
British Isles (B)					9	1	
Danish (D)						1	
English (E)							4
French (F)							
French Can- adian (FC)							
German (G)							
Irish (I)							
Italian (I)							
Jewish (J)							
Portuguese (P)							
Negro (N)							
Syrian (S)							

The findings of this survey of ethnic origin are summarized in Table 5. As would be expected from the make up of the general population in their area nearly half of the patients were derived recently or remotely from the British Isles 9 were pure British Isles 4 were pure English and 12 were pure Irish. The Irish well represented in the urban populations of the northeast, are also well represented in the present series.

Fifteen patients were 'old Americans' (following the definition by Hrdlicka 1925 see Table 5). Two of the group of 100 patients were Negroes. Both were born in the South and sent to us from there no conclusion may be drawn from this fact however since it may merely reflect the source of the data.

Of the 100 patients 27 were Jews (26 men and 1 woman), 1 was Syrian and 1 was Armenian. As compared either with the general American population where the proportion of individuals ultimately derived from the Near East is approximately 5 per cent or with the urban Boston population where it approaches 14 per cent this 29 per cent is highly significant. That the high ratio exists is general knowledge (Boas 1949). One may question whether the

males and 3 females)

MATERNAL NATIONALITY								
<i>French</i> (F)	<i>French Canadian</i> (FC)	<i>German</i> (G)	<i>Irish</i> (I)	<i>Italian</i> (I)	<i>Jewish</i> (J)	<i>Portuguese</i> (P)	<i>Negro</i> (N)	<i>Syrian</i> (S)
			1					
3		1	2					
1		1						
1		1	1					
	1							
		2	1					
			12	1				
				6				
					27			
						1		
							2	
								1

excess represents an artifact of sampling or a real difference in incidence due to genetic or cultural factors. In the series of previous investigators it has been questioned whether an excess of Jewish patients was due to a higher incidence of coronary heart disease or to a culturally conditioned drive to visit the top doctor. In the present series it is unlikely that such patterned behavior was responsible for the excess since the 100 patients represent not the private practice of one physician but the private and ward practices of a large number of physicians spread out over a large area as well as patients obtained through hospital records, the Veterans Administration and other sources.

Summary

Clinical impressions favor the opinion that coronary heart disease is a familial disease. There has however been little scientific documentation of these clinical impressions and since their implications are of the utmost importance for the control of the disease it was believed necessary to carry out studies in this area. Obviously only a very close follow up study of hundreds of families over

several generations will provide a definitive analysis. However, this study, which is cross sectional rather than longitudinal, did uncover certain clues and it is hoped that by a further follow up of both patients and controls more information will be obtained.

Since coronary heart disease is encountered often in young men it was reasoned that the patients might come from short lived families and therefore a survey of the ages of parental deaths was made. If in addition it was demonstrated that more parents of patients than of controls died of coronary heart disease then it could reasonably be suggested that this is a familial disease. It was shown that more of the mothers and fathers of the coronary than of the control group were dead. The differences in age at time of death were not statistically significant but it was shown that 37.1 per cent of the fathers in the coronary group compared with 18.5 per cent of the fathers in the control group died from coronary heart disease. There was no significant difference in the percentages of deceased mothers (9.8 per cent and 7.7 per cent respectively), a fact that is not surprising since coronary heart disease is a male disease and is rarely experienced by women until after the menopause. When however the data on other cardiovascular ailments were added to those for coronary heart disease it was clearly demonstrated that the death of both parents from some kind of cardiovascular disease was more common in the coronary group than in the control group (see Table 3).

As a further test for the thesis that coronary heart disease is a familial disease the cause of death of siblings of the coronary group was studied. Here it was found that 8.6 per cent of the siblings of the coronary group as opposed to 1.0 per cent of the siblings of the control group died from coronary heart disease.

On the basis of the evidence concerning the proportion of deaths and the causes of death in the parents and siblings of both groups it is reasonable to conclude that coronary heart disease is more likely to occur in families or individuals if mother, father or siblings have experienced the disease.

A problem which requires further work is the delineation of the hereditary pattern which predisposes to coronary heart disease. A follow up report on the status of the patients and unmatched controls at the end of 1953 is presented in Appendix F.

This chapter also considered racial susceptibility or immunity

to coronary heart disease. Since the actual number of cases studied was not great, specific conclusions pertaining to the general American population cannot be made. It may be noted, however, that there were in this group of patients a preponderance of Jewish individuals and a scarcity of Negroes.

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CHAPTER IV

Anthropometric and Morphological Appraisal of Physique

ASSOCIATIONS real or imagined between type of physique and cause of death have been claimed for many years, but despite the persistence of these claims specific correlations have remained undemonstrated. The robust pyknic physique has been more associated with cardiovascular disorders and the linear, asthenic type with respiratory disorders but individual predictions are hardly practicable (Sheldon 1940 Lessa 1943 Ciocco 1936 Bauer, 1945 Petersen, 1932)

On the other hand actuarial and biometric studies employing large numbers of individuals have all demonstrated that cardiovascular disorders are more frequent in individuals who are above normal weight than among those who are below normal weight. This general relation however is less well demonstrated in the female than in the male (Dublin and Marks 1938) and, even in the male the more carefully the physique is defined the less perfectly the generalization is maintained.

As these authors showed (1937) the mortality of tall overweight men is greater than that of short overweight men while the mortality of tall overweight men with short spines is far greater than that of tall overweight men with long spines. Thus within the general group of 'overweight' men certain physiques have a mortality over expectancy while other physiques still 'overweight' have no excess mortality. Pearl (1940) and Pearl and Ciocco (1934) also show that the more precisely a physique is defined the better the differentiation between disease groups. Thus in the present study the problem is to define the factors of physique and morphological character as sharply as possible in order to obtain optimum differentiation between those with specific disease predispositions and others not so predisposed.

Studies by Other Investigators

Since coronary heart disease has been recognized only rather recently as a disease of the younger adult and since such cases are infrequent in the private practice of any one cardiologist descriptions of the physique of the patients as a group have come in recent years only although many individual cases have been reported

Levine and Brown (1929) commented that young office patients with coronary heart disease had round thick wrists and other characteristics suggesting both musculature and rotundity The first survey of coronary heart disease in young individuals made by Glendy et al (1937) included a brief summation of physique According to their study which employed standards not defined the majority of these young patients were either obese or overweight only 30 per cent were average or lean French and Dock (1944) in a preliminary study of coronary heart disease in young soldiers also reported that the majority of 80 initial cases were overweight or obese The same trend was observed in a study by Goldsmith and Wilbus (1937) who found that in comparison with insurance company standards a group of patients who had experienced coronary thrombosis were significantly overweight Similarly McCam et al (1950) reported that 23 per cent of 281 autopsied cases of myocardial infarction were obese On the other hand Yater et al (1948) reporting on a very extensive Army series including French and Dock's 80 cases noted that the men who died ultimately after experiencing verified coronary atherosclerosis with infarction were often overweight at the time of induction but not at the time of death This important observation questioned the role of weight per se in the etiology of coronary heart disease and also raised the problem of whether weight reduction constituted any real preventive therapy Moritz and Zamcheck (1946) similarly showed that Army men who died after coronary occlusion were no heavier than Army men who died accidental deaths although both groups were "overweight" if norms based on inductee statistics were used This explained the findings of French and Dock (1944) while at the same time questioning the validity of the conclusions in earlier studies Overweight alone did not seem to be the factor

White (1944) on the other hand following Levine and Brown (1929) stressed as an etiological factor not fat or obesity but

rather the fact that many of his young male coronary patients were well muscled athletic and in a sense, the 'most masculine of men suffering at an unusually early age a highly sex limited disorder Newman (1946) observed the same physique factor in his British Army study the soldiers who developed coronary heart disease were fine physical specimens and ranked high on physical fitness scores

Thus various studies did suggest a physique factor in the etiology of coronary heart disease but the actual description of the physique was not formulated Despite this lack of agreement in the studies themselves most clinicians have assumed that fat is an etiological factor in coronary heart disease and have employed weight reduction for therapy

It was one of the purposes of the present study to investigate the physique of individuals who had experienced myocardial infarction from the standpoint not only of habitus and anthropological type but also of masculinity of build since it had been suggested by Draper (1941 1944) Seltzer (1945) Sheldon (1940 1949) and others that disorders with a higher incidence in the male are often more common in hypermasculine than in hypomasculine physiques The basic problems for investigation then, were

- 1 What physique distribution actually exists among individuals who have coronary heart disease at an early age?
- 2 Is obesity a prime etiological factor in this disorder?
- 3 Is there a coronary physical type?

Method of Appraisal in Present Study

The suggestions inferences and clinical hunches about the physical characteristics of the young male with potential coronary heart disease led to the formulation of a program designed to embrace most of these leads The program of physical appraisal was set up to investigate (a) the anthropometric characteristics of the coronary group determined by standard measurements (b) weight in the coronary group its relation both to accepted standards and to the weight of a comparable group of healthy males as well as coronary weight height ratios (c) the gross morphological character of the coronary patients in terms of physique habitus or body build

These programs of investigation were carried on by the methods

of investigative research used by physical anthropology. Weight and height weight data were gathered and subjected to analysis. Physique ratings were given first at the time of examination and later in revised form after inspection of standardized somatotype photographs which permit the simultaneous inspection of three views of the individual at once. Measurements were taken and studied and indices of proportions were calculated with a special view to obtaining a description of the thoracic region. Morphological traits were selected among the hundreds available to include such features of age as balding and graying such features possibly correlated with masculinity or virility as total hairiness and specific features relating to the configurations of the pectoral region the waist the hips and the thighs. Moreover other data possibly related to masculinity were included among the ratings (see Chapter VI). The problem of assessing masculinity objectively is an inordinately difficult one. Voice pitch and size of genitalia were noted but were not thought satisfactory for objective recording.

In all there were 24 measurements regularly made in addition to age 12 indices were used in the final report and 32 additional characteristics and morphological traits were rated (see Seltzer 1943 and Kovacs and Hartnung 1935 who also used anthropometry in the study of a disease population).

These individual ratings and measurements were separately related to the psychological hormonal biochemical and physiological studies in progress. The physical appraisal in the anthropological sense is considered in this chapter while the detailed considerations of the findings and their interrelations with other data are considered separately in this monograph and in other publications. Because of the probable unfamiliarity of the medical profession with the anthropometric methods involved they are presented in somewhat greater detail than they would have been in a report designed simply for an anthropological audience. These findings must be confirmed or refuted in terms of the methods employed. Were they not given in sufficient detail to allow other workers to test their reliability* it would be difficult to appraise their value satisfactorily.

* Reliability is here used in the sense employed in psychological testing. A reliable test is one that consistently produces the same results in the hands of different observers who employ the same methods. An "unreliable" test is one that may be internally consistent only in the hands of the same observer.

Anthropometric Findings

Measurements and indices used

In selecting measures for this study we desired contact measurements as close to the skeletal measurements as possible (so that there would be less age influence) as well as measures of both central mass and thoracic mass. In this way we could determine whether differences were (a) general, (b) concentrated in the thoracic trunk or (c) peripheral. In addition we desired to test specifically the alleged obesity of coronary heart disease patients by comparing the measurements of waist breadth and hip breadth assuming that abdominal flaccidity is the best single measure of this ill defined term obesity.

In addition to general measures we selected a few that show little variation with physique but do show racial differences. Thus it was possible to use race influenced measures as indicators of possible sampling errors.

The measurements of the thoracic trunk were four in number: chest depth (upper), chest depth (lower), chest breadth and chest length (sternum ensiform). There were four measurements of the peripheral region: hand length, hand breadth, wrist depth, wrist breadth. Ten measurements of the head and face were taken: bi-pupillary, nose length, nose breadth, upper face length, total face length, biocular, bizygomatic, bigonial, head breadth and head length.

Girths were not used because of the difficulties in determining the proper point of measurement in an older and usually plumper population.

MEASUREMENTS

Abbreviations

A = Anthropometer

SC = Sliding Caliper

Sp C = Spreading Caliper

Starred items are standard for anthropometric measurements (Hooton 1946, Martin 1928). Metric measures were used except for weight which was recorded in pounds.

- 1 *Age to past birthday
- 2 *Weight nude or with minimum clothing
- 3 Usual weight average weight in five years previous to examination as stated by the subject
- 4 *Stature maximum height to vertex
- 5 Span tip to tip arms fully extended A
- 6 *Shoulder breadth biacromial taken from the front A
- 7 *Chest breadth chest breadth at level of nipple moderate pressure A
- 8 Waist breadth waist minimum contact measurement A
- 9 *Hip breadth bi iliac A
- 10 Upper chest depth midmanubrium to spine anthropometer level A
- 11 *Lower chest depth sternum to spine at level of nipple moderate pressure A
- 12 Chest length (sternum ensiform) sternal notch to palpated bony tip of xiphoid process A
- 13 *Bipupillary interpupillary diameter with eyes relaxed S C
- 14 *Nose length nasion (by projection) to subnasale S C
- 15 *Nose breadth maximum bialar S C
- 16 *Upper face length nasion (by projection) to prosthion (by projection) S C
- 17 *Total face length nasion (by projection) to menton (moderate pressure) S C
- 18 Wrist breadth distal tuberosity of radius to distal tuberosity of ulna maximum measurement not at right angles to axis of forearm S C
- 19 Wrist depth contact measurement dorsal ventral at right angles to above S C (ordinarily)
- 20 Hand length third wrist crease to tip of index finger S C
- 21 Hand breadth at right angles to long axis of hand maximum base of digit II (index finger) to triquetral bone S C
- 22 Biocular (by palpation) right orbital border to left orbital border at level of fronto zygomatic suture Sp C
- 23 Bizygomatic maximum diameter across zygomatic crests Sp C
- 24 *Bigonial maximum diameter at gonial angles Sp C
- 25 *Head breadth maximum biparietal Sp C
- 26 *Head length from nasion toinion Sp C

INDICES

- 1 Ponderal index $\frac{\text{height (in inches)}}{\text{cube root of weight (in pounds)}}$ A measure of body mass such that the most massive physiques approach 100 and the most linear physiques approach 140. The massive physiques are relatively heavier per foot of stature.
- 2 Thoracic index $\frac{\text{lower chest depth}}{\text{chest breadth}} \times 100$ A measure of chest roundness, such that the roundest chests approach 100.
- 3 Relative span $\frac{\text{span}}{\text{height}} \times 100$ A measure of relative body length.
- 4 Hip shoulder index $\frac{\text{hip breadth}}{\text{shoulder breadth}} \times 100$ A measure of relative hip breadth such that indices of 85 or over indicate broad hips i.e. feminoid proportions.
- 5 Waist hip index $\frac{\text{waist breadth}}{\text{hip breadth}} \times 100$ A measure of the hip breadth such that indices under 80 indicate relatively narrow waists and somewhat feminoid appearance.
- 6 Upper facial index $\frac{\text{upper face length}}{\text{bizygomatic distance}} \times 100$ A measure of relative face breadth such that a broader upper face results in a lower index.
- 7 Eye face index $\frac{\text{bipupillary distance}}{\text{upper face length}} \times 100$ A measure of the relative eye face breadth such that a narrower interpupillary diameter results in a lower index.
- 8 Nasal index $\frac{\text{nose breadth}}{\text{nose length}} \times 100$ A measure of relative nasal breadth.
- 9 Shoulder index $\frac{\text{shoulder breadth}}{\text{height}} \times 100$ A measure of breadth of shoulders and therefore the reciprocal of linearity.
- 10 Hand breadth index $\frac{\text{hand breadth}}{\text{hand length}} \times 100$ A measure of linearity of hands.
- 11 Wrist breadth index $\frac{\text{wrist depth}}{\text{wrist breadth}} \times 100$ A measure of wrist roundness.

12 Cephalic index $\frac{\text{head breadth}}{\text{head length}} \times 100$ A measure of roundness of head most used in racial comparisons

Comparison of coronary and control groups

MEASUREMENTS The ages of the two groups compared very closely the average age of the coronary heart disease group being 38.2 years and that of the unmatched control group 36.7 years. The difference of +1.5 years in favor of the coronary group is small and does not attain statistical significance. Moreover changes due to age at this age level (35 to 40) are extremely small. As described in Chapter I the two groups were quite comparable in socio-economic status. Their differences lay in factors considered to pertain especially to coronary heart disease.

In addition to age and usual weight 24 measurements were made on both the coronary heart disease group and the unmatched control group. One of these the biocular was not used in the analyses that follow. Of the remaining 23 measurements 10 showed significant difference between the two groups—that is critical ratios (of the difference between the means) exceeding 2.5—while 3 others showed borderline significance—critical ratios equaling 2.0–2.5.

The 14 measurements in Table 1 in which the control group exceeded the coronary heart disease group reflect in general the trend of the control group to be taller and more linear than the coronary heart disease group. This difference is best seen in height (a difference of 4.5 cm), span, total face length, hand length, and chest length. Thus 7 of the 14 measurements in which the control group exceeded are length measurements.

In 9 measurements out of 23 (age, usual weight, and biocular omitted) the coronary exceeded the control group, although the control group was taller and longer. It is of real importance to note that 8 of these 9 measurements relate to breadth, the one exception being nose length, which shows a difference that is not significant. The two most significant depth measurements were those of the upper chest and wrist. Thus despite the tendency of the coronary heart disease group to be shorter, it was at the same time absolutely broader. Therefore indices relating breadth to length would in general show the relatively greater breadth of the coronary heart disease group. For the purposes of this study it has been our policy to keep such indices at a minimum.

TABLE IV-1 Anthropometric measurements of coronary heart disease group of 97 males and unmatched control group of 146 males

	Coronary group mean \pm S.E.	Control group mean \pm S.E.
Age (years)	38.2 \pm 5	36.7 \pm 8
Weight (lbs.)	170.5 \pm 2.3	177.0 \pm 2.0*
Length measurements		
stature (cm.)	171.8 \pm 6	176.3 \pm 7†
span (cm.)	176.5 \pm 11	179.6 \pm 6*
chest length (cm.)	21.5 \pm 2	22.4 \pm 2†
nose length (mm.)	56.7 \pm 4	56.2 \pm 3
upper face (mm.)	68.4 \pm 5	69.6 \pm 4
total face (mm.)	121.1 \pm 6	123.6 \pm 6†
hand length (mm.)	191.2 \pm 9	193.8 \pm 6*
head length (mm.)	193.8 \pm 8	195.7 \pm 6
Breadth measurements		
shoulder breadth (cm.)	39.2 \pm 2	40.1 \pm 2†
chest breadth (cm.)	30.0 \pm 2	30.2 \pm 2
upper chest depth (cm.)	19.5 \pm 2	18.5 \pm 2†
lower chest depth (cm.)	23.0 \pm 2	22.5 \pm 2
hip breadth (cm.)	29.5 \pm 2	29.7 \pm 1
waist breadth (cm.)	29.5 \pm 2	29.4 \pm 2
hand breadth (mm.)	88.8 \pm 5	88.0 \pm 4
wrist breadth (mm.)	58.9 \pm 4	58.6 \pm 3
wrist depth (mm.)	41.1 \pm 3	39.9 \pm 2†
bipupillary (mm.)	62.8 \pm 3	65.4 \pm 3†
nose breadth (mm.)	36.7 \pm 3	36.1 \pm 2
bizygomatic (mm.)	141.1 \pm 6	141.0 \pm 4
bigonial (mm.)	107.3 \pm 5	108.2 \pm 4
head breadth (mm.)	153.8 \pm 6	154.6 \pm 5

*Difference significant

†Difference highly significant.

The two groups were also compared with respect to their homogeneity for these anthropometric measurements that is their standard deviations were compared. No important differences were noted except that the control group was more variable with respect to height. However, when height was compared with weight (ponderal index), there was no difference in absolute variability.

INDICES Twelve indices were regularly employed in comparing the two groups. In general, they were chosen as having special utility in physique comparisons. Two of the 12, however (nasal and cephalic indices) were selected as having the least to do with physique and relating rather to racial differences.

The indices in Table 2 were derived by analyzing statistically the original indices computed for each individual (that is they were based on primary measurements, not on group averages).

TABLE IV-2 Anthropometric indices in coronary heart disease group of 97 males and unmatched control group of 146 males

<i>Index</i>	<i>Coronary group mean \pm S.E.</i>	<i>Control group mean \pm S.E.</i>
Ponderal	12.25 \pm .06	12.43 \pm .05
Thoracic	76.8 \pm .6	74.4 \pm .5†
Relative span	102.9 \pm .4	101.8 \pm .2
Hip shoulder	75.5 \pm .5	74.3 \pm .4
Waist hip	99.9 \pm .7	98.3 \pm .4‡
Upper facial	48.7 \pm .4	49.5 \pm .5
Eye face	92.2 \pm .7	94.1 \pm .6
Nasal	65.1 \pm .7	65.0 \pm .5
Shoulder	22.9 \pm .1	22.8 \pm .1
Hand breadth	46.3 \pm .5	45.3 \pm .3‡
Wrist breadth	69.6 \pm 1.0	68.2 \pm .7
Cephalic	79.3 \pm .6	79.0 \pm .5

Difference significant.

†Difference highly significant.

‡Borderline significance

Table 2 indicates that the coronary heart disease group showed a uniform trend toward relatively greater depth and breadth. Of the 12 indices there were 4 with significant differences and 2 others with borderline significance. The coronary heart disease group was higher than the control group in 4 of these 6 indices and in 1 other index (ponderal) showed greater breadth by a decreased index. In only 1 index (eye face) did the control group appear to have the significantly higher value. If statistical significance is disregarded, 10 out of 12 indices showed a tendency to greater breadth on the part of the coronary heart disease group.

Two of the significant indices are the ponderal and the thoracic. Their differences well illustrate the evidence that the coronary heart disease group was relatively heavier per foot of stature and that it showed central distribution of weight. The distribution of the two groups according to ponderal index is given in Table 3.

The relative hand breadth and the relative span also showed important differences. The difference in relative hand breadth confirms the observational impression of lower linearity in the coronary heart disease group. The control group had relatively longer narrower hands.

The waist hip index shows that the coronary heart disease group despite its greater mass was not marked by a significantly broader waist.

In contrast to the significant differences discussed above the

TABLE IV-3 Distribution of ponderal indices in coronary heart disease group of 97 males and unmatched control group of 146 males

Ponderal index	CORONARY GROUP		CONTROL GROUP	
	No	%	No	%
10.5-10.9	0	0.0	1	0.7
11.0-11.4	4	4.1	4	2.7
11.5-11.9	24	24.8	29	19.8
12.0-12.4	39	40.3	46	31.5
12.5-12.9	20	20.7	47	32.2
13.0-13.4	8	8.2	13	8.9
13.5-13.9	2	2.0	4	2.7
14.0-14.4	0	0.0	2	1.4

cephalic and nasal indices do not show significant differences. These indices are in general of utility in racial analysis rather than in physique analysis and help to confirm the evidence that the two groups were relatively similar except in the respects noted.

Indices are especially indicative of trends, for not being absolute measurements they eliminate differences in absolute size between the two groups. Thus the difference in proportion continues to be evident both centrally and peripherally.

EVALUATION OF WEIGHT Because of the attention now given to the term: overweight and the concept of obesity especially as they might affect the etiology and prognosis of myocardial infarction it is well to review these terms before evaluating the weight factors in the present study.

Overweight is at best a statistical concept referring to gross weight in excess of some standard selected for comparison.

Obesity is on the other hand a morphological concept referring to softness, corpulence and fatty deposits (obese excessively corpulent, very fat—*Webster's New International Dictionary*). Although it is possible to set objective standards of obesity so that individual judgments can be validated as by the use of the McCloy fat calipers (McCloy 1936) ordinarily no such standards are set and the interpretation is dependent to a large degree upon the personal bias of the investigator which in turn is a function of his experience and clientele. Despite this objection to the term the concept of obesity has real pertinence in clinical study for one can view directly the encompassing fatty deposits and decide whether the subject is carrying more fat than is useful. This firsthand evaluation is far superior to any table of norms.

The difficulty of rating obesity and the even greater difficulty of trying to make the rating on the cadaver or from hospital records rather than directly have led to the practice of making determinations of overweight as a measure of obesity. Overweight ratings may customarily mean (a) any value above an arbitrary norm (b) some fixed value above a norm or (c) some fixed percentage above a norm. Furthermore, overweight must be considered in terms of the individual and it is obvious that the simple word overweight does not describe physique.

McCloy states the same problem *

This normal weight must be interpreted in terms of the individual's build. The slender linear type of individual is and should be lighter in weight for the same height than the stocky lateral type of individual. For purposes of predicting what this normal weight should be, some standards must be devised. These will be primarily measurements involving the size of the skeleton both as to dimensions of the thoracic cage and hips and as to the thickness or coarseness of the long bones. Only when the standard weight has been computed from such fundamental bases can under- and overweight be considered significant enough to be used in directing the hygienic regimen.

The second measurement of nutritional status is the relative amount of fat. The amount of fat underlying the skin needs to be measured and a norm or standard found to determine whether or not the fatty deposits of any given individual are greater or less than the optimum amount. Fat also enters into the problem of under- and overweight but it is partly a factor to be measured and interpreted separately.

The third measurement used in nutritional status studies is that of the normal development of muscle. This will be considered under two general headings: (1) muscle as it makes up the general nutritional background of the body and (2) muscle as an organ for strength. It is well established that muscular development is one of the factors determining adequate weight for any given type and the lack of this muscular development is frequently associated with chronic poor nutrition.

Sheldon writes on the problem of differential weight norms †

We do a great unkindness to those trusting people who still believe in the divinity of the printed word when we allow the usual publications

*C. H. McCloy, *Appraising Physical Status: The Selection of Measurements*. University of Iowa Studies in Child Welfare, 1936, pp. 33-34. Quoted by permission of the publishers.

†W. H. Sheldon, S. S. Stevens and W. B. Tucker, *The Varieties of Human Physique*. Harper & Bros., New York, 1940, p. 26. Quoted by permission of the publishers.

sitated a physique rating system marked by the following features

- 1 It would follow the concept of morphological constitution—the principle that the individual's bodily habitus is unchangeable once it is established (Williams, 1933), distinguishing between habitus and nurture
- 2 It would be age corrected so that age and nutritional features would not be confused with constitutional differences, nor would one age be used as a standard for all ages
- 3 The individual would be rated numerically and without reference to types
- 4 The ratings would show useful correlations

Somatotype method

While the vast majority of physique rating systems (Kretschmer's Violas and others) have employed bipolar or even tripolar typologies thus necessitating a few extreme or pure types and a large mixed category the Sheldonian system of somatotyping makes use of three polar extremes only as directions and designates the various combinations in terms of distance along the three directions

To quote Sheldon (1940) : "Physique is a continuum and any system of rating must have as its purpose the location of the individual on the three dimensional spectrum of physique" The numerical rating system in the Sheldonian method performs that function. Thus the rating in the Sheldonian sense avoids typology though the terminology makes it possible to designate the position of the physique in words as well as in numbers

In this system each individual is given a rating expressed in three numbers, each representing the *relative dominance* of one physique component or direction. The highest number represents the dominant component the next highest number the secondary component, and the lowest the least prominent component. The three number rating thus immediately assigns the individual to his position on a tri coordinate physique spectrum (Sheldon 1940 1942 1949 Hooton 1945, 1946 Seltzer 1943 1946 1948 Seltzer and Brouha 1943 Bullen and Hardy 1946)

According to the conventions of the system the minimum number for each component is set at 1 (that is each component must be represented to some degree) and the maximum is set at 7. Thus

The difficulty of rating obesity and the even greater difficulty of trying to make the rating on the cadaver or from hospital records rather than directly have led to the practice of making determinations of overweight as a measure of obesity. Overweight ratings may customarily mean (a) any value above an arbitrary norm (b) some fixed value above a norm or (c) some fixed percentage above a norm. Furthermore, overweight must be considered in terms of the individual and it is obvious that the simple word overweight does not describe physique.

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of height weight age norms to go unexplained. It is sorrowful to hear the lament of a [woman] who is already 30 pounds overweight, but who reads daily on the printed scales that she is 30 pounds underweight. And the poor [man] who weighs 99 pounds reads with horror that he should weigh 178. This kind of foolishness gives some of our best people inferiority complexes and then they have to be analyzed or sent to church.

In order to study the problem of 'overweight' we have followed the method of Levy et al. (1946) and have computed the deviation between a norm (for height and age for each person) and the actual weight. This has been accomplished for the coronary heart disease group and for the unmatched group of 146 controls as well.

The comparison between the coronary heart disease patients and the unmatched controls was also made in terms of five year age groups—21–25, and so on—with reference to the appropriate norms. Both the coronary heart disease patients and the controls showed excessive weight with reference to the Army norm. The amount of excessive weight varied from age group to age group being largest in the 26 to 30 year category. However the pattern of excess weight by age group was essentially the same in the coronary heart disease group and in the unmatched control group. The average deviations from the Army norms were $+19.1 \pm 1.9$ pounds and $+18.5 \pm 2.1$ pounds respectively (Garn, Gertler, Levine, and White, 1951).

Such criteria must be based on factors of age, sex, body build and height. The Army standards of age, height and weight partially fulfill these requirements and the resulting weight norms can serve as a baseline with which any group or groups may be compared. If two groups have been thus compared with the baseline it is then valid to compare them with each other. This was done in the present study with the result that both the coronary and the unmatched control groups showed approximately the same degree of overweight with respect to the Army norms. Since the unmatched controls represented a good cross section of the American population the logical implication is that the whole American male population is overweight. The unsatisfactory nature of norms that suggest the deviation of an entire population from normal is evident. However until more adequate criteria are developed these norms serve as a valid baseline for comparison of data.

Rating of Physique

As indicated previously a major problem for consideration in this study is neither weight nor overweight nor even obesity itself but rather a comparison of the physical characteristics of two groups to determine whether the differences or similarities in weight and in weight indices may be due to different proportions of constituent tissues. In other words the problem is physique rating. There are three possible methods of rating: (1) dividing the individuals into discrete typological entities or types (2) dividing some single continuum such as that of height/cube root of weight into equal intervals or (3) employing a new system forming a continuum.

The first or typological classification is based on physique appraisal with or without the supplementary aid of anthropometric measurements or indices. Kretschmer's typologies (1925-1945) are perhaps the best known example. In the system of this Bavarian clinician there are the following types: (a) pyknic (b) athletic (c) asthenic and (d) mixed. The pyknics are robust and florid, the asthenics are linear, the athletics are well muscled but linear, and the mixed category is what it implies. Thus the system widely used in medical studies presents individuals in terms of discrete categories. Its major disadvantage is that the mixed group usually includes most individuals and the system makes no allowances for age changes; that is, with advancing years and corpulence more individuals end up in the first category at the expense of the athletic, asthenic, and mixed categories. Williams, writing in Cowdry's *Arteriosclerosis* (1933), asks pertinently whether some observers have confused the appearance of good nurture and obesity with that of the sthenic habitus.

McCloy (1936) and his associates have analyzed Kretschmer's system (1925-1945) by means of indices, especially the height/cube root of weight index. They find no evidence of bimodality (which would be true if there were two populations, one of laterals and one of linears). However, although McCloy and his co-workers favor a constitutional appraisal based on the height/cube root of weight index, they also hold to the idea of linear and lateral types, with this addition—that due attention and correction should be made for fat and muscle. Willoughby (1932) has devised ideal weight standards similarly based on structure for the adult.

It was apparent then that the requirements of this study neces

sitated a physique rating system marked by the following features

- 1 It would follow the concept of morphological constitution—the principle that the individual's bodily habitus is unchangeable once it is established (Williams 1933) distinguishing between habitus and nurture
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In this system, each individual is given a rating expressed in three numbers each representing the *relative dominance* of one physique component or direction. The highest number represents the dominant component, the next highest number the secondary component, and the lowest the least prominent component. The three number rating thus immediately assigns the individual to his position on a tri coordinate physique spectrum (Sheldon 1940 1942 1949 Hooton 1945 1946 Seltzer 1943 1946 1948 Seltzer and Brouha 1943 Bullen and Hardy 1946)

According to the conventions of the system the minimum number for each component is set at 1 (that is each component must be represented to some degree) and the maximum is set at 7. Thus

each of the three numbers in the system may theoretically vary between 1 and 7. However the components necessarily show inter correlations such that a change in any one component usually shows a corresponding but not necessarily equal change in one of the other two (for example if one man is more muscular than another he is likely to be less linear). The order of components in the three digit numbers is always the same: endomorphy, mesomorphy, ectomorphy (these may be referred to as the first, second, and third components respectively).

The names of the three components are selected to recall the primary germ layers that are in part represented in them, though it should be stressed that the names are largely mnemonic devices and should not be taken to imply that a component refers entirely to a particular germinal layer (Hunt 1949).

Endomorphy is the component of softness, roundness, and smoothness but not necessarily fat. An endomorph may be a rounded, smoothed-off individual without being frankly obese, though the extreme endomorph usually becomes obese. Diagnostic features include blunt chin, neck angle, deep round thorax, pneumatic appearance, hamming of upper arms, juxtaposition of thighs, and (usually) genu valgum, small features, and anteroposterior diameters greater than transverse.

Mesomorphy is the component of muscularity, bone mass, angularity of outline and contour. A mesomorph has large bones and joints (and is thus recognized even in age), a sharp chin, neck angle, a deep thorax, good shoulder muscles, usually a triangular shoulder to hip tapering in both sexes, heavy leg muscles, and broad hands. Even combined with considerable endomorphy, the mesomorph is still easily distinguishable.

Ectomorphy is the component of linearity, fragility, elongation. The ectomorph has long fingers, long toes, long narrow hands and feet, a long frequently shallow thorax, long femora, often a pinched waist. The extreme ectomorph is distinguished from the merely emaciated individual by these structural criteria.

Rating is accomplished from the standardized, carefully posed photograph, together with height-weight data (using a table for certain age levels), data on the patient's health history, and preferably a view of the subject himself. Research somatotyping has as its purpose the rating of the individual's potential in physique.

and should not be attempted without available medical data. This is especially important in the study of a disease group (such as the present) where the patients are of varying ages and where it is necessary to determine whether these patients have physique factors in common.

After viewing the standardized photographs and the other data the *dominant* component is first determined by inspection or (when difficult) after referral to previously rated photographs. Then the *secondary dominance* is determined. Finally the numerical ratings are applied. Usually when the dominance is recognized, its degree is immediately apparent. This is not always the case however the subject may be a 7 (extreme) in endomorphy, but the secondary (mesomorphic) component may require further study to determine whether it is a 3 or a 2.

It will be seen that this method of rating differs from others used previously by noting not only the direction (dominance) but also the distance along that direction to which the physique extends. A 7-1-1 and a 4-3-3 are both dominant endomorphs but the difference is major. Not always is one component clearly dominant in some cases two components may be about equal, as in the 5-5-1 the 4-4-2 and others. In still other and rarer cases all three components are about equal or balanced such is the 4-4-4 a mean but by no means modal physique. Typical ratings are

Dominant endomorphs 7-1-1 7-2-1 7-3-1 6-2-2 6-3-1,
5-4-1

Dominant mesomorphs 1-7-1 2-6-2 3-5-3 4-5-1, 2-5-4

Dominant ectomorphs 2-2-6 1-1-7 1-2-7 2-3-5, 2-4-5

Mid ranges 4-4-4 4-4-3 4-3-3 3-3-4 3-4-4

While the numbers immediately fix the position of the individual on the tri coordinate somatotype triangle and it is possible to visualize the approximate location of any physique against this triangle for convenience in speaking and writing it has been agreed to employ the principal dominance as a noun and the secondary modifying dominance as an adjective. Hence in the latter part of this chapter we will call a person who has a 4-6-1 physique an *endomorph* *mesomorph* (meaning a mesomorph with endomorphic modification) one who has a 6-4-1 physique a *mesomorph* *endomorph* and so on.

Certain physiques are easy to rate at any age these include the extremes—1-1-7 7-1-1 1-7-1—as well as the other polar physiques. Other physiques are much more difficult for the inexperienced to rate at older age levels. This is especially true of the endomorphic mesomorphs and mesomorphic endomorphs. Both are quite round in the late forties. But when one is compared with the other the difference becomes quite apparent it is a function of the strength of the second (mesomorphic) component. The mesomorphic endomorph like the dominant endomorph is round pneumatic and we find often a difficult subject for venipuncture. But the endomorphic mesomorph though paunchy is high paunched frequently still rugged in outline. We include examples of the differences between these physique groupings * (See below under Classification by Dominances or Types for other examples of the coronary heart disease physiques.)

The physiques 7-2-1 7-3-1 6-3-3 and the like are frequently difficult to distinguish in later age groups because they are all fat and the supporting mesomorphy is difficult to assess. However in our coronary heart disease group such mesopenic endomorphs are rare.

Method used in present study

In the course of this study it has been possible to employ not only the information provided by the immediate appearance of the individual but also all the valuable data provided by the interview the health history and the information provided on occupation and athletic interests. Naturally far more data were obtained on the young coronary heart disease patients (who were subjected to an intensive interview) than on the controls. However in the unmatched control group records were made of the weight at 21-25 years of age maximum weight occupation and athletic interests therefore the final ratings were based on a more detailed knowledge of the individual than his momentary appearance alone would have provided.

PROCEDURE FOR EXAMINATION With the available information the rating was made in the following manner

*On the other hand it has been shown by Lasker (1947) that the accurate somatotyping of starvation cases is difficult. Luckily only one of the cases in the present group comes under this heading.

- 1 The weight and height were taken
- 2 Anthropometric measurements were made
- 3 The patient's weight and health history were considered
- 4 Ratings of body configuration were made
- 5 The somatotype photograph was taken
- 6 The patient was kept on the somatotype stand the spot points were noted and, after palpation of the patient an impression somatotype was made usually after a concurrence by the two observers
- 7 After the printed photograph was returned, the impression somatotype was corrected, if necessary This rarely required shifting of component dominance and usually consisted of adjustment between two closely related somatotypes e.g. 3-5-2 and 4-5-2

In the course of this work we learned that some of the inspectional criteria used by Sheldon (1940) were applicable to all age levels Most conspicuous of these were

- 1 Trapezius development
- 2 Chin-neck angle
- 3 Development of clavicles
- 4 Biceps and triceps form with the arms in the somatotype position
- 5 Triangular form of the torso (dorsal view)
- 6 Relative shoulder-hip size
- 7 Sacral angle (back curve)
- 8 Relative torso-leg length

On the other hand criteria that applied to softness of outline (endomorphism) were less applicable in our groups (which were about twenty years older than his) except for the somatotype low in endomorphy

It has been our experience with the impression somatotype that fairly good ratings of the second (mesomorphic) component are possible since the general configurations—muscularity of legs arms shoulders and back—are all visible and palpable but that the first (endomorphic) component is apt to be underestimated especially in the older male Since a number of the referring physicians were interested in our rating system we were curious to see how their appraisals correlated with our own The only marked discrepancy appeared with ectomorphic mesomorphs who were considered by them to be ectomorphs probably because they were more familiar with the typology of Kretschmer (1945)

TABLE IV-4 Dominant physiques in coronary heart disease group of 97 males and unmatched control group of 146 males

	<i>Coronary group</i> <i>n</i>	<i>Control group</i> <i>n</i>
Endomorphs	25 7	29 9
Mesomorphs	42 2	19 8
Ectomorphs	7 3	21 1
Mid range	17 5	18 4
Two balanced	7 3	10 8

CLASSIFICATION BY DOMINANCES OR TYPES As a first rough sorting the individual ratings were divided into

- 1 Dominant endomorphs—6-2-2 6-4-1 5-3-3 and so forth
- 2 Dominant mesomorphs—2-5-3 4-5-1 2-6-2 and so forth
- 3 Dominant ectomorphs—2-4-5 2-3-5 2-2-6 and so forth
- 4 Mid range physiques—4-4-4 3-4-4 4-4-3 and so forth
- 5 Two balanced somatotypes—5-5-1 2-4-4 and so forth

This preliminary sorting was done to see if there was evidence that major differences existed in one component. It was especially important to see whether the coronary heart disease group showed more endomorphs in view of the data presented earlier in this chapter.

As shown in Table 4 there was evidence that the coronary heart disease group and the control group differed in the distribution of their dominant components. The major differences (see Figures 1 and 2) occurred within the category of dominant endomorphy; the differences between the percentages showing secondary mesomorphic and ectomorphic components were statistically significant. The percentages falling into the category of endomorphy as a whole however showed no significant difference.

It was noted that the ectomorphs in the coronary heart disease series were entirely mesomorphic ectomorphs—that is, well muscled linear men.

To summarize in comparison with the control group the coronary heart disease group showed

- 1 About the same proportion of dominant endomorphs
- 2 About twice as many dominant mesomorphs
- 3 Less than half as many dominant ectomorphs
- 4 About the same proportion of mid range physiques
- 5 About the same proportion of two balanced physiques

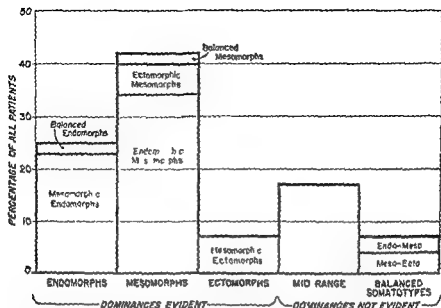


FIGURE IV-1 Distribution of physiques among 97 young male coronary heart disease patients. In this group the mesomorphs were the most common while ectomorphs were surprisingly rare.

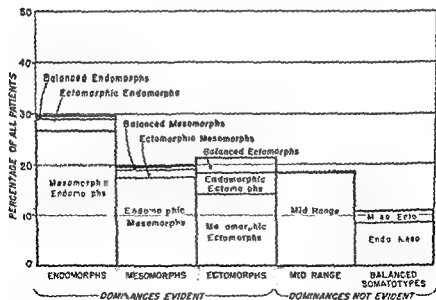


FIGURE IV-2 Distribution of physiques among 146 unmatched controls. In this group the endomorphs had a slight predominance.

FIGURES 3-9 SHOW THE VARIETY OF
SOMATOTYPE RATINGS FOUND IN THE
CORONARY HEART DISEASE GROUP

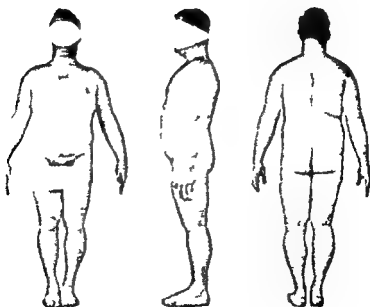


FIGURE IV-3 Somatotype endomorphy 5 1/2 mesomorphy 6 ectomorphy 1 Age
29 height 5'8 1/2 weight 137 lbs

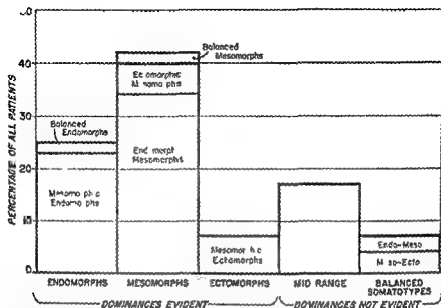


FIGURE IV-1 Distribution of physiques among 97 young male coronary heart disease patients. In this group the mesomorphs were the most common while ectomorphs were surprisingly rare.

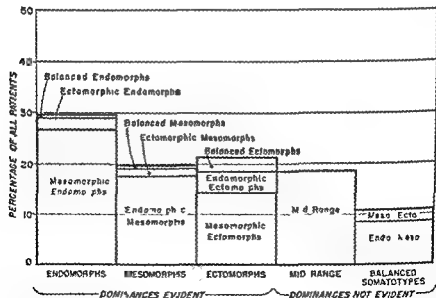


FIGURE IV-2 Distribution of physiques among 146 unmatched controls. In this group the endomorphs had a slight predominance.

FIGURES 3-9 SHOW THE VARIETY OF
SOMATOTYPE RATINGS FOUND IN THE
CORONARY HEART DISEASE GROUP

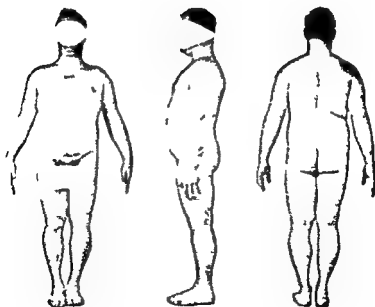


FIGURE IV-3 Somatotype endomorphy 5 1 - mesomorphy 0 ectomorphy 1 Age
29 height 5' 8 1/2 weight 137 lbs

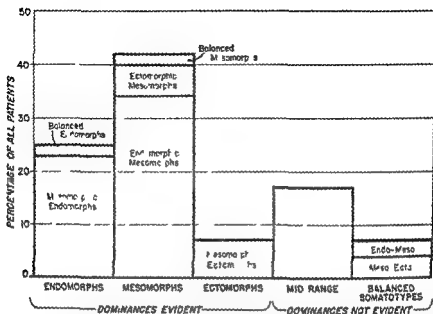


FIGURE IV-1 Distribution of physiques among 97 young male coronary heart disease patients. In this group the mesomorphs were the most common while ectomorphs were surprisingly rare.

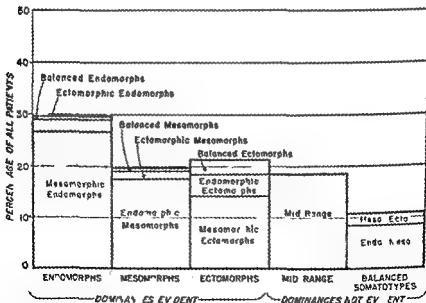


FIGURE IV-2 Distribution of physiques among 146 unmatched controls. In this group the endomorphs had a slight predominance.

FIGURES 3-9 SHOW THE VARIETY OF
SOMATOTYPE RATINGS FOUND IN THE
CORONARY HEART DISEASE GROUP

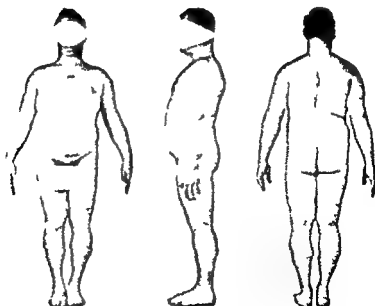


FIGURE 3 Somatotype endomorphy 5 1 - mesomorphy 6 ectomorphy 1 Age
9 1 - ht 5 8 1 - weight 137 lbs

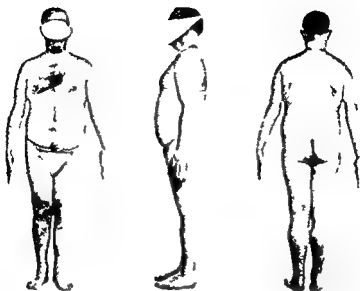


FIGURE IV-4 Somatotype endomorphy 5 mesomorphy 4 1/2 ectomorphy 1 Age 37 height 5'2" weight 152 lbs

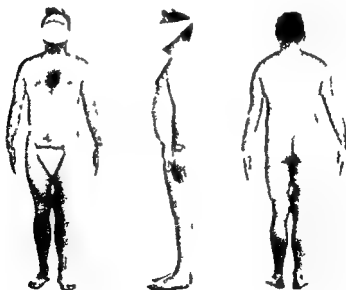


FIGURE IV-5 Somatotype endomorphy 5 mesomorphy 4 1/2 ectomorphy 1 Age 38 height 5'3" weight 160 lbs

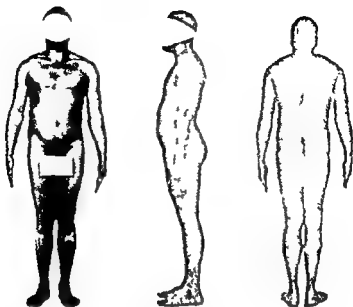


FIGURE IV-6 Somatotype: endomorphy 2 1 mesomorphy 5 1 ectomorphy 2 1/- Age 39 height 5' 7 1/2 weight 180 lbs

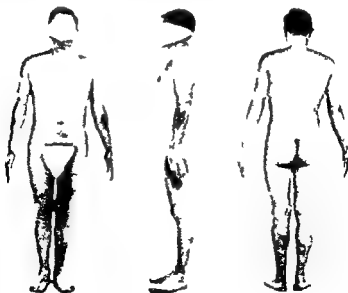


FIGURE 1-7 Somatotype: endomorphy 3 mesomorphy 6 ectomorphy 1 Age 41 height 5' 6 weight 175 lbs

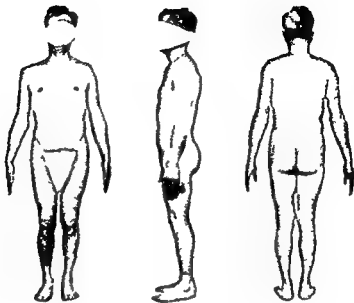


FIGURE IV-8 Somatotype endomorphy 3 mesomorphy 4 ectomorphy 3 Age 36 height 5'5" weight 162 lbs

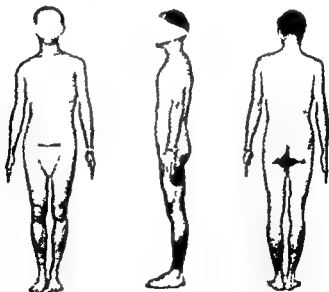


FIGURE IV-9 Somatotype endomorphy 2 mesomorphy 3 ectomorphy 5 Age 25 height 5'5" weight 130 lbs

Figures 3 through 9 illustrate the variety and range of component ratings observed in the coronary heart disease group

It is of some interest to note also the physique of the 3 female patients who are not included in the rest of this discussion Two women were dominant mesomorphs whose secondary dominance was endomorphy The third was a dominant ectomorph with secondary mesomorphy

DISTRIBUTION OF CORONARY GROUP As mentioned before physique is represented as a three dimensional continuum in the somatotype system The method of dividing the somatotypes into dominant endomorphs mesomorphs ectomorphs and mid range physiques may therefore be misleading for it forces more rigid categorization than is absolutely necessary To the advanced worker such a fourfold division smacks too strongly of the familiar rigid types and the defects of the Kretschmerian system In our present study we can also see that the arbitrary separation of endomorphic mesomorphs from mesomorphic endomorphs creates a dichotomy not found in nature Thus the preceding section though illustrative of the relative frequency of certain physiques in the continuum requires more careful interpretation

An alternative method devised by Sheldon which is probably superior to the fourfold division is that of plotting the distribution of cases directly on the somatotype triangle Here adjacent points are related somatotypes whether the dominances are the same or not As we mentioned earlier the components are directions and the equal interval increments are distances along these directions Thus for a two dimensional surface the three components can be represented by three equal length vectors and the resultant figure is shown to be a triangle (Sheldon 1940 p 118) On this figure any somatotype can be plotted according to its vector position and then read

When we plot the 97 young male patients in the coronary group we note a clumping in the upper left sector of the triangle an absence of peripheral positions and a concentration in the mesomorphic sector We see that the distribution of coronary heart disease cases clumps in the massive muscular northwest corner

In contrast our control group of 146 males shows a more general distribution a wider spread and a more equitable division (though with some degree of skewing)

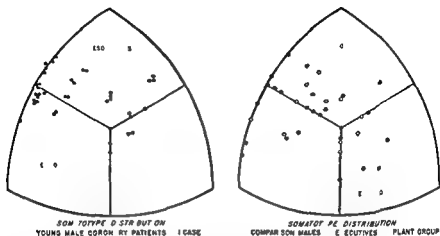


FIGURE IV-10 Somatotype distributions of coronary heart disease group of 97 males and unmatched control group of 146 males. The patients showed a marked deficiency in ectomorphy and a deficiency in endomorphy. The physique distribution in their group was more compact.

The distribution in the lower region of the somatotype triangle is especially noteworthy while the endomorphs and ectomorphs with low mesomorphy are well represented in the control group the comparable area is blank for the coronary heart disease group (Figure 10)

Summary

There has long been speculation concerning the relation between body build, body weight and longevity. The trends of thought on this topic have always been concerned with an association between (a) longevity and leanness and (b) cardiovascular disease and obesity. The definitions of overweight, leanness and obesity have not been entirely satisfactory. Accordingly this study attempted to delineate overweight and body build in a more definitive manner. Body weight in the coronary heart disease group and in the control group was compared with a weight norm for age and height computed from Army standards. From this comparison it was demonstrated that the coronary heart disease group was not overweight in relation to the control group. By employing the Sheldon system of physique classification it was learned that coronary heart disease is significantly associated with a specific body

habitus rather than with body weight. These body types were further delineated by careful anthropometric measurements. It was clearly demonstrated that the endomorphic mesomorph—the fat muscular person—is most prone to coronary heart disease while the ectomorph—the lean person—is the least prone to coronary heart disease.

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CHAPTER V

Athletic Activity and Occupations

Athletic Activity

A NUMBER of previous investigators had reported that athletic histories were common among those who experienced coronary heart disease early in life (Levine and Brown 1929 White 1944 Newman 1946) In order to elaborate on these reports and to investigate athletic participation more thoroughly all the coronary patients in the study were questioned as to their previous athletic activities Because athletics is an integral part of the American scene and the majority of males have participated in some sport at some time in their lives, the interview was carefully conducted in order to separate casual players from regular participants in organized athletics

First each man was asked whether he had participated in athletics during grammar school If the reply was affirmative he was asked what sports had been involved and to what extent and whether the teams had been intramural or interscholastic The same questions were repeated for the period of secondary education The men were asked whether they had been on regular high school teams and whether they had won letters or similar awards Those who had gone to college were queried in a similar manner Lastly the question of professional or semiprofessional athletics was brought up

In the event of negative replies the interviewer attempted to discover whether the lack of participation was involuntary or voluntary Involuntary non participation was recorded when the subject's school had no athletic programs when he had to work on the farm or support the family or when non participation was forced by chronic disease It is noteworthy that two men who had not been allowed to participate in school athletic programs because of a history of rheumatic fever later participated extensively in club and local athletics

TABLE V-1 Athletic records of coronary heart disease group of 97 males

<i>Athletic activity</i>	<i>No. of patients</i>	<i>%</i>
GRAMMAR SCHOOL		
Went to grammar school but not beyond	20	100
highly athletic* in grammar school	3	15
not athletic in grammar school but athletic in later life	4	25
HIGH SCHOOL		
Went to high school but not beyond	46	100
starred in major athletics†	23	50
starred in minor athletics	12	26
unable to participate had to work	8	17
unable to participate poor health	3	7
COLLEGE		
Went to college	31	100
starred in college major athletics†	5	16
unable to participate had to work	2	6

*Participated in all the organized sports the school allowed

†Baseball and football

The men in the coronary heart disease group were divided into three categories (a) those who did not go beyond grammar school (b) those who did not go beyond high school and (c) those who completed college. Accordingly the athletic histories were completed for the highest educational level, that is if a man went through college he was not included in either the high school or grammar school group. The results are tabulated in Table 1.

In the high school category, 50 per cent starred in major athletics. This proportion appears to be unusually high in contrast to the total percentage of boys who received one or more letters in football at the high schools attended by many of the coronary heart disease patients in Providence and Boston. In these schools 10.05 per cent from a group of 1,091 received letters. At Harvard University 6 per cent of the students received letters in major sports, a somewhat lower proportion than the 16 per cent in the coronary heart disease group who received letters for major athletics while attending college.

Six of the total group of 97 patients went on to semiprofessional or professional athletics. Another was a skilled competitive skier. Many others remained interested in athletics after their school days and participated in soccer, volleyball, and other club or Y M C A sports.

There appears to be an association between the coronary condi

tion and the athletic participation. It must not be concluded, however, that athletics and coronary heart disease are causally related. It is not to be said that participation in athletics is responsible for the myocardial infarction. Rather the athletic histories of these individuals is a function of their mesomorphy and the large number of ex athletes in the series is related to the disproportionate number of mesomorphic individuals in the series. In fact the most athletic individuals in the group did have the highest average mesomorphy score 4.85.

Thus it may be concluded that (a) among the patients in this series there appears to be an unusually large proportion with athletic histories as measured by regular participation and awards in the contact sports (baseball and football) as well as in less organized individual sports (skating and so on) (b) the high degree of athletic participation is in accord with the predominance of mesomorphic individuals in the series and (c) coronary heart disease and athletic participation may well be related only through the common factor of mesomorphy.

Occupations

Various views are held about the possible relationship of economic position and occupation to the development of coronary disease. These range from the view of Brock Chisholm who reiterates the commonly held idea that diseases of the in manager are disproportionately a disability of the rich to frequency of (1949) and Boas and Donner (1932) who have observed how- it disease to be surprisingly frequent among talents may aug- the fact that these groups were Jewish may in- tions who are al- since it is known that the disease is more include hereditar- population. Unfortunately the many con- ances in lipid met- complicated by the fact that the sorting d that in some studies women are in s they are not. Moreover racial data occupational groupings are made in e- n of the kind of work involved te (1939) surveyed 3 400 unselected chusetts General Hospital and found clusion (but not of acute coronary in private patients as in ward patients

BOAS E. P. *Coronary Artery*

BOAS E. P. and DONNER

98 2186-2189 1932

CHISHOLM B. *Social medicine*

GORDON W. H. BLAND E. F.

Journal of the American Heart Association

versely if a and BROWN C. Y.

115-418 1929

we assume that

Thus a selection made for the most part on a purely economic basis gave a highly significant indication. Master et al (1939) classified 938 cases of coronary heart disease on the basis of occupation and concluded that there was no great occupational difference in incidence. However the incidence was somewhat higher in the professional and business group than in the total series.

Yater's study of a large series of Army personnel (1948) showed an association between the pre Army occupation, both rural and urban and the disease state. Our group did not have the opportunity to study any individuals with coronary heart disease selected primarily because they were of rural origin; most of the patients were city dwellers.

In the present study we have investigated the suggestion that supervisory personnel are unduly prone to the disorder a suggestion that comes not only from Yater's series but also from Dunbar's work and our own interview data. It was our impression throughout the interviews that these patients wanted to succeed in anything they attempted and furthermore that they were able to do so.

The occupations of the 97 males in our series are given in detail in Appendix E. (Although 13 men were in the armed forces at the time of their coronary episodes their pre service occupations were listed since in all but three cases their peacetime activity other than that of professional soldier.) The distribution of major occupations is given in Table 2 according to the following contrast to

- I Executive and managerial owner and operator of business enterprise with policy and executive function or other persons in charge with the supervision of the activities of others in schools 10 05
- II Professional physician lawyer architect and other persons employed and without general managerial functions in major sports
- III Semiprofessional specialty salesman medical technician trained factory technician major athletics while
- IV Skilled machine worker
- V Semiskilled maintenance mechanic electrician to semiprofessional
- VI Unskilled factory worker and competitive skier

The major distinction in this classification is between those after their school days (those in charge of others) and Classes II to VI. Other club or Y M C A occupations are not at a managerial and direct supervision. A lawyer with an active staff would be in the coronary condi-

TABLE v-2 Occupational classifications of coronary heart disease group of 97 males

Class	No of patients
I Managerial	42
II Professional	11
III Semiprofessional	7
IV Skilled	4
V Semiskilled	30
VI Unskilled	3

lawyer without a staff would be in Class II A sales manager would be in Class I a salesman in Class III

It is evident from the table that the coronary heart disease group is not confined to any one occupational class The proportion of cases falling into the managerial and executive classes appears to be very high 42 out of 97 cases (There has long been a clinical impression that there is a bias in this direction) It is unfortunate that we do not have available for purposes of comparison a sample of the general male population selected in a manner similar to that of the coronary heart disease group It is believed that this inordinately large increase in managerial and executive groups is larger than one sees in the general population

This analysis points to two important facts (a) coronary heart disease is not confined to any one occupational class and (b) those in managerial and executive positions do exhibit a relatively high frequency of appearance in this series of patients It should be observed however that factors other than executive and managerial talents may augment the number of individuals holding such positions who are among the coronary patients These factors would include hereditary influences hormonal imbalances and disturbances in lipid metabolism

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 we assume that

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Certain causal relations have been invoked to explain the higher incidence of coronary heart disease among males. These etiological factors may be divided into three groups: (a) physical differences, (b) hormonal differences, and (c) genetic differences.

There are claims that the male temperament, environment, and habits require a greater expenditure of energy and that this difference in energy output is primarily responsible for the higher incidence of coronary heart disease among males (Pearl 1931). Such an assumption based on differences in physical energy alone is not supported by evidence. Possibly the excess of energy output is an expression of other factors that would be harmful in themselves even if the energy output could be controlled.

Similarly, not all the attributes of maleness that may govern predisposition to coronary heart disease need be imputed to gonadal secretions and sex hormones (see Chapter VII). These secretions maintain a highly active state of function in various tissues with resultant increase in body metabolism and influence: (a) male behavior to some extent (Beach 1948), (b) steroid metabolism with specific reference to cholesterol (Sayers et al. 1943), and (c) degree of intimal permeability. However, there is no definite evidence that the androgens exert any specific deleterious action on the coronary arteries.

In some individuals a relative change in certain characteristics such as degree of aggressiveness, submissiveness, and docility does occur with the amount of androgenic material available. Thus C. C. Hawke reports 90 male castrates studied in Kansas who were originally docile, agreeable, submissive, and cooperative became recalcitrant, disagreeable, intractable, and uncooperative as the daily dose of testosterone was increased.

The genetic influence is considered in greater detail in Chapter III. It is sufficient to say here that the hereditary aspect probably includes additional factors which may be (a) autosomal, (b) autosomal but hormonally mediated, or (c) autosomal combined with other sex-linked factors that may or may not be hormonally mediated. The differentiation between sex-linked and hormonally mediated disorders is sometimes difficult to determine, and coronary heart disease may be one of these borderline conditions. Thus the genotypes that govern predisposition to coronary heart disease may be suppressed by gynogenic hormones and evoke coronary condi-

genic hormones The Kansas study referred to above of 90 males who were castrated at ages varying from prepuberty to middle age may shed light on the male predisposition to coronary heart disease for these castrates are males genetically but not hormonally

Masculine and Feminine Characteristics

In evaluating masculine and feminine characteristics one could employ several lines of study such as psychological responses physical characteristics hormonal assays and others For practical purposes however none of these characteristics will produce a clear cut separation of the sexes even though the hormonal aspects of masculinity and femininity are fairly well established (see Chapter VII) and anthropologists have shown certain physical differences to exist between males and females—body build voice hair distribution and pelvic measurements

The psychological characteristics of men and women overlap to a very large extent Although it is undoubtedly true that the traits of both sexes are influenced by physical differences it has not been proved conclusively that any characteristic is wholly innate uninfluenced by training and environment So complex are the interrelations between biological and environmental factors that it is impossible in the light of present knowledge at least to say more than that men and women in our culture respond in certain general ways with statistical consistency (see Appendix A) Thus men do react more consistently with aggressiveness and women with docility but how far through innate or acquired responses we cannot say

When it comes to definitely acquired characteristics the distinction between the sexes becomes less and less apparent Thus love of fine art and music is a common meeting ground enjoyment of books dealing with intellectual interests rather than with adventure or homemaking is a mutual experience

In an effort to provide some sort of rating scale for psychological differences exhibited by men and women without attempting to evaluate the innateness of the traits revealed Terman and Miles (1936) devised a test which is useful in determining to what extent an individual fits the typically masculine or feminine pattern of our culture Both the coronary patients and their matched controls were given this test as a part of this study we assume that

Terman Miles test

The test is divided into parts A and B * each of which contains seven sections. Each section contains questions word associations or other types of data that are considered to distinguish the typically masculine or feminine characteristics of an individual of either sex. The typically masculine elements are scored as plus the feminine as minus and neuter as zero. The average scores for male college athletes and engineers as studied by Terman and Miles are + 92 and + 77 respectively while average scores for dressmakers and grade school girls are — 104 and — 95 respectively. Women holding M.D. and Ph.D. degrees scored an average of — 34. The seven exercises of the Terman Miles test are

- 1 Quadruple choice word associations
- 2 Ink blot associations
- 3 Information test
- 4 Emotional and ethical responses
- 5 Interests likes and dislikes
- 6 Personages and opinions
- 7 Introvertive responses

RESULTS The average scores obtained by 70 of the 97 males in the coronary heart disease group and by a matched control group of 70 males are summarized in Table 1

The coronary patient group scored significantly less (15 points lower) on the average for all seven exercises than did the matched control group. In the individual exercises the coronary disease group scored significantly less in Exercises 3 and 6. Exercise 3 is the general information test a multiple choice questionnaire calling for an exact knowledge of fact that is dependent upon the experience and interests of the subject. The test revealed that the coronary heart disease patients as a group were somewhat less aggressive, adventurous enterprising and self assertive than the control group. They were actively sympathetic and concerned with domestic affairs art and literature. Exercise 6 has two sections one calling for expression of attitude toward selected historical personages and the other for judgment concerning the truth or falsity of certain statements. Generally speaking it may be stated that in preferring

* Usually the average sum of the scores on test A and test B is the final score. But this is not necessary since either test alone may cond. Test A was employed throughout this study.

TABLE VI-1 Mean scores on Terman Miles test made by coronary heart disease group and matched control group each of 70 males*

Exercise	No of cases	Coronary group mean \pm S E	No of cases	Control group mean \pm S E
1	70	— 5.3 \pm 1.0	70	— 7.6 \pm 0.9
2	70	+ 0.2 \pm 0.3	70	— 6 \pm 0.3
3	70	— 0.4 \pm 1.2	70	+ 9.4 \pm 0.6†
4	70	+ 26.6 \pm 2.8	70	+ 33.2 \pm 1.8
5	70	+ 13.9 \pm 1.8	70	+ 12.5 \pm 1.5
6	70	+ 1.4 \pm 1.0	70	+ 5.4 \pm 0.6†
7	70	+ 0.4 \pm 0.7	70	— 1.0 \pm 0.5
TOTAL	70	+ 36.0 \pm 4.7	70	+ 51.2 \pm 2.8†

*27 tests in each group were not completed for diverse reasons

†Significantly greater

famous women, unfortunate people, and philanthropists rather than successful generals, sports heroes, and defiers of convention, and by thus favoring kindly sentiments that made allowances for disabilities such as their own. Our coronary patients again showed a more typically female pattern.

INTERPRETATION These results may appear to be surprising in view of the fact that many of the coronary patients have been described as tending to be hard driving and determined to succeed. The apparent contradiction, however, has several possible explanations. The very fact that these men were able to push through to success in their enterprises may well have put them in a position to participate increasingly in the more cultural aspects of our society, thereby modifying their interests and attitudes in the direction considered more typically feminine. Furthermore, at the time of testing, most of the patients had experienced some degree of invalidism which in itself might lead to the adoption of more sympathetic attitudes and more sedentary and intellectual interests.

One may seriously question whether the characteristics usually associated with psychological masculinity or femininity influence the susceptibility of the individual to coronary heart disease. Even though we have found that the typical patient originally showed masculine traits that were later modified toward the feminine, can we assume that, in general, overt characteristics of masculinity in a healthy male are indicative of covert characteristics which may enhance his susceptibility to coronary heart disease? And conversely, if a healthy male shows overt feminine characteristics, can we assume that these are indicative of covert characteristics which

may confer protection against the disease? Hamilton (1948) has stated that he avoids the often tempting but naive tendency to ascribe all conditions associated with one sex solely to the temperaments habits or environments of the members of that sex. However whether or not such characteristics as aggressiveness boldness and love of adventure are causally related to coronary heart disease they may possibly be expressions of some hormonal factor that may be linked intimately with the etiology of the disease.

Relation of Morphological Findings to Aging and Masculinity

There were a number of suggestions that the young male prone to coronary heart disease might show (a) characteristics of premature aging or (b) excessive development of masculine characteristics or excessive response to androgenic stimuli. In the first case the assumption was that coronary heart disease is a concomitant of age and that therefore the individual who shows this condition at an unusually early age must be prematurely aged. The second hypothesis is based on the known disproportionate ratio of males to females with coronary heart disease at this age level and it was suggested that since coronary heart disease is masculine those who have it earliest are *ipso facto* more masculine. Both questions could be investigated by analyzing morphological findings. Were the first suggestion true—that the young patients in our series were prematurely aged—we could anticipate excessive balding excessive graying and other concomitants of age such as arcus senilis temporal arteritis and calcification of the aorta. If the second were true—that the patients showed unusual responses to androgenic stimuli or produced unusual amounts of androgenic substances—we could anticipate excessive development of body hair musculature and so forth and a minimum of gynandromorphic characteristics. Accordingly the following characteristics were rated.

- 1 Hair graying balding, and body hair
- 2 Body form size of genitalia gynandromorphy pectoral development thigh interspace knee interspace hip roundness waist curvature and pectoral development

Rating methods and results

SCALP HAIR Each of the items (see Figure 1 and Table 2) was rated separately on a 5 point scale ranging from a minimum of zero

FINDINGS ON MASCULINITY

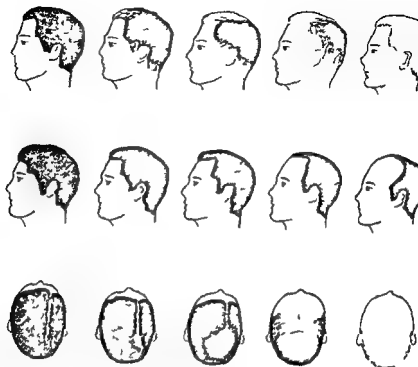


FIGURE VI-1 Hair rating: five degrees of graying (top), frontal balding (center), and tonsorial balding (below)

TABLE VI-2 Hair rating

Item	Rating	Description
Hair graying	0-4	0 no graying or a few gray hairs
		4 totally or nearly white
Frontal balding	0-4	0 no frontal notch balding
		1 frontal notch balding
		2 enlarged notch recession
		3 near complete frontal
Tonsorial balding	0-4	4 total frontal balding
		0 no tonsorial balding
		1 thinness over occipital whorl
		2 definite circle balding
Combined balding	0-8	3 enlarged circle balding
		4 tonsorial "Hippocratic fringe"
		Total of frontal and tonsorial ratings

TABLE VI-3 Percentage of coronary heart disease group of 97 males and of an matched control group of 146 males whose hair rating was 1 or more

	Coronary group %	Control group %
Graying	40	45
Frontal balding	95	95
Tonsorial balding	44	41
Combined balding	95	95

to a maximum of 4. Certain items—total balding, total hair, and total areas—are totals of others and thus may have more points on the scale.

Although the rating method is admittedly subjective, the use of a 5 point system proved satisfactory and highly reproducible. Certain ratings, such as a zero or a 1 or a 4 in frontal balding, can be made by any observer without previous practice (see Figure 1 and Table 2). The majority of the ratings showed high correlations between the two observers (Garn 1951).

As Table 3 shows, there was no evidence of increased graying in the coronary group. The chi square test indicated no difference in the distribution of graying. Frontal balding, tonsorial balding, and combined balding showed no significant differences. Hence there was no evidence that the young coronary disease population was either grayer or balder or more prematurely aged in these respects.

BODY HAIR. The rating employed for body hair is given in Table 4. Again a 5 point scale was used.

In general, findings revealed the body hair of the young coronary heart disease group was slightly greater than that of the unmatched control group, but this difference was not significant in most of the regions examined. In certain regions (thoracic, lower arm, upper arm, thigh, leg, sacral, and upper back) the greater hairiness of the coronary heart disease group almost attained statistical significance by the chi square test. Analysis of midphalangeal hair patterns showed more individuals in the coronary than in the control group who (a) had no such hair (45.3 per cent versus 37.7 per cent) and (b) had more hair on the fourth finger alone (18.9 per cent versus 12.3 per cent). By and large, however, these facts merely reflect a greater percentage of Mediterranean peoples in the coronary group (Bernstein and Burke 1942).

TABLE VI-4 Body hair rating

<i>Item</i>	<i>Description</i>
Beard	0 absent 1 mustache chin beard 2 mustache chin beard cheek beard 3 mustache chin beard cheek beard (heavy) 4 extends to intraorbital region
Abdominal	0 absent 1 linea alba triangle 2 spread 3 over rectus to costal angle 4 covering rectus obliques to sides
Thoracic	0 absent 1 circum areola or sternal 2 spread over chest nearly to deltoids 3 axilla 4 total to deltoids and axilla
Lower leg arm	0 absent 1 over dorsal aspects only 2 spread lightly 3 dorsal same ventral hands 4 total all aspects feet and hands
Upper leg arm	0 absent 1 slight dorsal 2 marked development 3 nearly to hips shoulders 4 total coverage to deltoids and gluteal region
Gluteal	0 absent 1 anal cleft 2 extended 3 skin nearly covered 4 total dense
Sacral	0 absent 1 few hairs 2 marked 3 marked triangle 4 dense
Lower back	same ratings as for Sacral
Upper back	same ratings as for Sacral
Midphalangeal	individual fingers noted
Total hair	total of all above ratings (0-40)
Total areas	no. of areas rated 1 or more (0-10)

TABLE VI-5 Body hair in coronary heart disease group of 97 males and unmatched control group of 146 males

	CORONARY GROUP		CONTROL GROUP		Difference	Significance	Chi square
	Mean \pm S.E.	Mod	Mean \pm S.E.	Mode			
Total of body hair ratings	12.80 \pm 7	12	11.30 \pm 7	8-10	+1.50	1.5 ns	*
No. of areas in which hair was observed†	6.90 \pm 2	6	6.10 \pm 2	6	+ .80	2.8*	

Ns—Not significant

*Significant

†Beard abdominal thoracic lower arm, upper arm thigh leg, gluteal sacral, lower back, and upper back.

When the scores for all ten areas were totaled the average was 12.80 for the coronary heart disease group and 11.30 for the unmatched controls (see Table 5). The difference is suggestive but not clearly significant.

Of the ten areas examined the average number scoring 1 or more in the coronary heart disease group was 6.9 and for the control group 6.1. Again the difference was suggestive but not clearly significant.

BODY FORM In distinction to the rating of hair, the characteristics of body form were rated on a 4 point scale.

TABLE VI-6 Body form rating

Item	Description
Gynandromorphic index	Feminoid appearance in general configurations
Texture index	(See Sheldon 1940)
Thigh interspace	Degree of thigh juxtaposition 1 no space 4 maximum space
Knee interspace	1 no space 4 maximum space
Hip roundness	1 narrow or straight hips 4 broad round hips
Waist curvature	Incurvation of waist 1 minimum 4 maximum
Pectoral development	Fatty development over pectoral region 1 no fatty development 2 slight softness 3 mammary development 4 distinct breast formation

There were a number of differences in detailed morphological characteristics between the coronary heart disease group and the unmatched control group but these differences which appeared to be spotty and form no regular pattern tended to be explained as partial functions of the somatotype

In the broader aspects of body form significant differences between the two groups were found in the following variables texture index thigh interspace knee interspace hip roundness waist curvature and pectoral development These findings are summarized in Table 7

The coronary heart disease patients were found to have slightly finer texture and slightly rounder hips The slight excess of hip roundness they displayed may be explained by the marked deficiency in ectomorphy and the excess of endomorphic mesomorphy in the coronary group

Similarly the lower degree of ectomorphy in the coronary heart disease group can account for less knee and thigh interspace as compared with the control group It is the ectomorph and the mesomorphic ectomorph who have the cowboy legs

The increased mesomorphy in the coronary group apparently also resulted in less waist curvature than was shown by the control group

Hence the following differences may be attributed to higher mesomorphy in the coronary heart disease group (a) less thigh interspace (b) less knee interspace (c) more hip roundness and (d) less waist curvature

TABLE VI-7 Body form in coronary group of 97 males and unmatched control group of 146 males

	Coronary group mean \pm S.E.	Control group mean \pm S.E.
Gynandromorph index	1.29 \pm .07	1.19 \pm .04 n.s.
Texture index	2.26 \pm .10	2.01 \pm .06*
Thigh interspace	1.48 \pm .11	1.76 \pm .07
Knee interspace	1.41 \pm .11	2.1 \pm .07†
Hip roundness	1.38 \pm .08	1.17 \pm .04
Waist curvature	.77 \pm .09	1.10 \pm .03†
Pectoral development	.95 \pm .08	1.37 \pm .05†

N.s.—Not significant.

*Significant.

†Highly significant.

Summary

Why is the male more prone to coronary heart disease? Does masculinity predispose toward the disease? If so, how is masculinity to be assessed? The problem is complicated by the necessity of choosing characteristics which will permit comparison of discernible degrees of difference. Is the appraisal to deal with hormonal makeup that is the excess of testosterone in the male? Can the evaluation be based on body build? Or can masculinity be measured in psychological terms by determining differences in attitudes? These questions were considered in making our study. No definitive answers emerged but several findings are noteworthy.

In relation to hormonal makeup there was no evidence that excessive androgens predispose toward or produce coronary heart disease.

In morphological makeup the study indicated the coronary patients were more masculine than the controls.

Psychologically the coronary group showed attitudes that are considered more typically feminine than those of the control group. A possible explanation for the apparent conflict of this finding with the masculinity of physique is that both the cultural milieu into which the typical drive of these men may take them and the physical inactivity enforced by their illness may modify their outlook in a more cultural and sympathetic direction.

Thus it may be suggested that the coronary individual studied in this group is a male with a high component of physical masculinity that is probably due to inherited characteristics but whose mental attitudes are tempered either by illness or by the acculturation to which he is exposed by virtue of his driving psychological makeup.

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CHAPTER VII

Endocrine Findings

THE hormonal aspects of masculinity have been the subject of broad and intensive studies by Allen (1934) Hamilton (1948) and others. The present study at first aimed simply to assess the hormonal aspect of masculinity by a survey of urinary 17 ketosteroid excretion. Although this was known to provide a very crude estimate of androgenic activity it was believed that any deviation from the expected norm in the amount of daily excretion might suggest a parallel change in androgenic secretion by the adrenals and the testes. This is discussed at greater length later in the chapter.

In addition however another aspect of hormonal appraisal was carried out—determination of thyroid status. This was appraised by means of (a) basal metabolic rate (b) radioactive iodine urinary excretion and (c) various serum lipid interrelations. Since coronary heart disease is more common in individuals with hypercholesterolemia and since hypercholesterolemia and hypothyroidism are often associated it was decided to determine the degree and extent of thyroid influence on this elevated level of serum cholesterol.

17 Ketosteroids

The measurement of androgenic and estrogenic material by biological tests is not sufficiently specific to be entirely satisfactory (Fraser et al. 1941). However this difficulty was partially overcome by Callow's modification of the Zimmerman technique of determining 17 ketosteroids. It should be emphasized that not all androgens are chromogenic and conversely, not all chromogenic materials possess androgenic activity. For example etiocholan-17-one 3α -ol is a 17 ketosteroid but not an androgen while testosterone is an androgen but not a 17 ketosteroid. The chromogenic reaction and hence chemical specificity of the 17 ketosteroids depends upon a property of the grouping ($\text{CH}=\text{CO}$) containing an

active methylene group on the carbon at position 17 of the steroid nucleus, namely the ability to produce in the presence of meta dinitrobenzene a red color which may be analyzed quantitatively by the use of a photoelectric colorimeter with a green filter having a maximal transmission at 5120 Å

The 17 ketosteroids (sterone) are part of the metabolic products of both the adrenal and testicular glandular secretions excreted in the urine. The values considered normal for male adults vary from 6 mg to 22 mg of sterone per 24 hour urinary excretion while the values for females are lower (5 mg to 15 mg of sterone per 24 hour urinary excretion). The most difficult problems in this determination today are (a) fractionation of all the steroids excreted in the urine that possess androgenic activity and (b) differentiation of the amounts of androgens excreted by the adrenal cortex and by the testes.

No attempt was made in this study to fractionate the urine either into androgenic material or the alpha and beta ketosteroids as has been done by Salter et al (1946) or Hamilton and Hamilton (1948). Accordingly this study will give no insight into the adrenal as compared with the testicular contribution of the 17 ketosteroid excretion.

The values of the urinary sterone of 87 males who had experienced coronary heart disease are listed in Table 1. The influence of chronic debility on 17 ketosteroid excretion in the coronary heart disease patients is probably not an important factor since these patients are not debilitated in the usual sense of the word and are not the usual chronically ill type. Although they have experienced an illness they have made a good recovery so far as muscle tonus and general physical welfare are concerned (Barrabee 1950). The sterone excretion in the coronary heart disease group in Tables 1 and 2 and Figure 1 is compared with that of a healthy group compiled by Dr Fuller Albright and Dr Anne P Forbes in the Massachusetts General Hospital. These controls were laboratory assistants, physicians, normal soldiers and several members of the maintenance staff of the hospital. The data are comparable with ours, the determinations having been made by the same laboratory. The average age of the 87 men in the coronary group who had 17 ketosteroid determinations was 36.4 years and of the 50 in Albright and Forbes control group 28.4 years.

From the data included in Table 1 it is interesting to note that the difference between the mean 24 hour urinary sterone excretion of the coronary group and that of the control group is not significant in spite of the difference of approximately ten years in average age. If the data for the coronary heart disease group were corrected for age using the information in Table 2 the difference between the means would be even less.

Relation to age

There is evidence to suggest that the 17 ketosteroid urinary excretion begins to decrease at the age of 30 (Hamilton and Hamilton 1948, Venning and Kazmin 1946). Furthermore Hamilton and Hamilton state *

The major part of this decline is due to a loss of alpha ketosteroids which accounts in general for over 90 per cent of the total quantity of urinary ketosteroids. The curve of decrease in alpha ketosteroids parallels closely that for the total output of ketosteroids.

Our results shown in Table 2 are consonant with these observations: there is a significant decrease in 17 ketosteroid excretion during the course of the fourth and fifth decades.

Relation to other variables

The 17 ketosteroids are closely involved with many other variables in the human organism both in the normal and in the diseased state (Dobriner et al 1948). It seemed advisable to establish if possible the relations of the urinary ketosteroids to other variables examined during the course of this study. The correlation coefficients ranged from -19 to $+19$. None were statistically significant. They included correlations between 17 ketosteroids and age, height, weight, ponderal index, endomorphy, mesomorphy, ectomorphy, uric acid, phospholipids, cholesterol, basal metabolic rate and gynandromorphy. Those approaching significance were age (-19 ± 11), basal metabolic rate ($+19 \pm 11$) and gynandromorphy (-19 ± 11).

The correlation between 24 hour urinary 17 ketosteroid excretion and endomorphy, mesomorphy and ectomorphy was further investigated by comparing the 24 hour urinary sterone excretions

*Howard B. Hamilton and James M. Hamilton "Ageing in Apparently Normal Men" *J Clin Endocrinol* 8:451 1948

TABLE VII-1 24 hour urinary sterone excretion in coronary heart disease group of 87 males* and control group of 50 healthy males (Albright and Forbes series)

Sterone m†	Co onary g oup		Cont ol group	
	No		No	
2	1		0	
3	4		0	
4	5		1	
5	5		3	
6	4		3	
7	6		2	
8	8		7	
9	13		7	
10	10		5	
11	9		5	
12	8		3	
13	3		3	
14	1		3	
15	1		2	
16	2		3	
17	3		2	
18	1		0	
19	1		0	
20	1		0	
21	1		1	
	Ster one mg		Ster one mg	
Mean	9.9		11.1	
Standard deviation	4.2		3.7	
Range	2.4-21.0		4.9-21.6	
Standard error	0.44		0.54	

Urinary excretion of sterone was not measured in 10 male patients.

†Amounts are given to the last whole milligram.

TABLE VII-2 24 hour urinary sterone excretion by age decades in coronary heart disease group of 87 males and control group of 50 healthy males (Albright and Forbes series)

Age decade	No of cases		STERONE, MG	
			Range	Mean \pm S.E.
20-29	Coronary	6	3.9-18.5	11.5 \pm 2.36
	Control	27	5.4-21.6	12.2 \pm 0.85
30-39	Coronary	49	4.1-21.0	10.7 \pm 0.57
	Control	19	4.9-19.6	11.6 \pm 1.1
40-49	Coronary	32	2.4-15.0	8.6 \pm 0.56
	Control	4	5.6-18.5	11.2 \pm 1.90

Urinary excretion of sterone was not measured in 10 male patients.

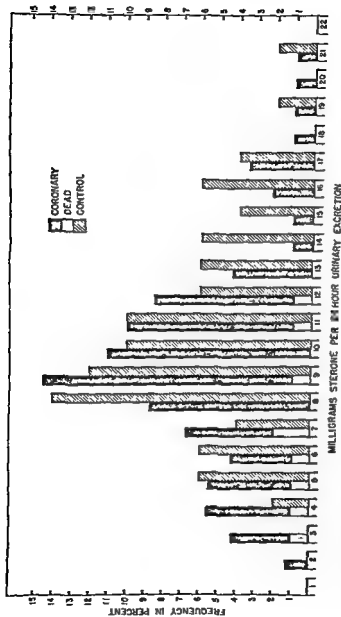


FIGURE 1. 4 hour urinary steroid excretion by 87 coronary heart disease patients and 50 unmatched controls. It is to be noted that those in the coronary group who died showed on the whole lower steroid excretion than those who survived (see also Table 4).

TABLE VII-3 24-hour urinary sterone excretion by physique in coronary heart disease group of 87 males*

<i>Predominant physique</i>	<i>No of cases</i>	<i>Ste one mg m an \pm S E</i>
Endomorphy	21	9.98 \pm 0.95
Mesomorphy	39	10.56 \pm 0.66
Ectomorphy	8	8.88 \pm 1.35
Mid range	19	9.25 \pm 0.77

Urinary excretion of sterone was not measured in 10 male patients

for the individuals in these three classifications. However, as might be anticipated from the other correlations, no significant differences were found. The exact values are listed in Table 3.

Relation to death in coronary patients

The values of urinary 17 ketosteroids were obtained in 9 men and 1 woman approximately two to four months prior to their deaths. The woman patient had a 24-hour 17 ketosteroid excretion of 2.2 mg. The values for the 9 men are listed in Table 4 (see also Figure 1).

It is noteworthy that in the coronary heart disease group the difference between the means of the surviving males (10.1 ± 0.42) and of the males who died (7.68 ± 1.02) is just barely significant. The decrease in 17 ketosteroids is interesting and merits further attention. The exact mechanism of this decrease will be unknown until better methods are available for distinguishing whether the components of the 17 ketosteroid fraction are adrenal or testicular in origin.

TABLE VII-4 24-hour urinary sterone excretion of 9 males who died from coronary heart disease

<i>Case no</i>	<i>Ste one mg</i>
17	12.5
31	7.8
III	3.9
47	7.3
49	11.8
63	4.1
64	5.8
69	9.3
71	6.6
Mean \pm S E.	7.68 \pm 1.02

Summary

The average 24 hour urinary sterone excretion in 87 young coronary patients was found to be lower arithmetically but not to a statistically significant degree, than that of 50 healthy controls who were on the average ten years younger the means and standard errors being 9.9 ± 0.44 mg per cent and 11.1 ± 0.54 mg per cent. This fact is interesting in that one would expect a significantly lower 24 hour sterone excretion in the coronary group on the basis of age alone for it is fairly well accepted that sterone excretion decreases with age. On the other hand, if any true alteration in sterone excretion accompanied coronary heart disease the average differences would be even greater with the coronary heart disease group showing an even lower daily sterone excretion. This point should not be dismissed lightly in spite of the age difference between the groups the average daily sterone excretion of both groups was nearly the same.

Those in the coronary group who died revealed a lower mean daily sterone excretion than those who were living at the time of this appraisal 7.68 ± 1.02 ($p = 0.05$) as against $10.1 \pm .42$ mg per cent.

These findings may be of some value in providing an objective basis for the assessment of the status of the patient following a myocardial infarction. If these data are substantiated by further follow up and study the method may prove to be much more objective and useful than any now employed. A routine periodic survey of 24 hour urinary sterone excretion would enable the physician to follow changes in the excretion pattern and if it showed a perceptible decrease then it theoretically should be possible to institute replacement therapy even if the classical ominous symptoms of coronary heart disease were not apparent.

The interrelations between daily urinary sterone excretion and other attributes such as age, basal metabolic rate, various physical components and biochemical variables were found to be statistically insignificant on the basis of coefficient correlation data although certain coefficients of correlation approached significance namely those of age, gynandromorphy and basal metabolic rate which were found to be -19 ± 11 , -19 ± 11 , and $+19 \pm 11$ respectively.

Thyroid Function

There has been little published in medical literature concerning the thyroid status in coronary heart disease. Blumgart et al (1933-1950) have attempted to produce a state of hypothyroidism by means of total ablation or radioactive iodine in order to improve the cardiac status in coronary or myocardial insufficiency by decreasing the cardiac output and hence the work of the heart. In 1946 J. Lerman and P. D. White suggested that the thyroid status of coronary heart disease patients under the age of 40 tends generally to be in the direction of a low basal metabolic rate. Since their series was small and further tests confirming this initial impression were desired by Lerman and White, additional studies on the thyroid aspects of coronary heart disease were incorporated in the present general study. Starr et al (1934) studied 11 patients (3 of whom were females, all in the seventh decade) but their series is also too small to merit evaluation.

The thyroid status may be gauged by means of various tests. The question of which is the best test has not been answered clearly. Probably Means (1948) has best epitomized the situation.*

To say that any one of these procedures is better or worse than another as an index of thyroid function is meaningless. They measure different things. Each throws light on thyroid function but from different angles.

Basal metabolic rate may be said to be an index of the total impact of thyroid hormone upon all its end-organs. Level of protein bound iodine is an expression of thyroid hormone concentration in the blood. Uptake of labeled iodine is an index of the thyroid gland's avidity for that element.

The values of the blood lipid levels in hypothyroidism and in hyperthyroidism have been the subject of discussion for many years. In general it is stated that serum cholesterol rises during hypothyroidism and decreases during hyperthyroidism (Mason et al 1930). However the observation on this point by Peters and Man (1943) is noteworthy. They accept but modify Mason's dictum†

Although cholesterol rises when the thyroid gland is removed and

J. H. Means *The Thyroid and Its Diseases* 2nd ed. J. H. Lippincott Co. Philadelphia 1948 p. 167. Quoted by permission of the publishers.

†John F. Peters and Evelyn B. Man "The Interrelations of Serum Lipids in Patients with Thyroid Disease" *J. Clin. Invest.* 22:719 Sept., 1943.

falls when active thyroid preparations are given normal concentrations of cholesterol may be found in the serum of patients with hyperthyroidism or with thyroid deficiency because the level to which cholesterol falls or rises with these disorders is roughly related to the normal cholesterol concentration of the affected subject

An excellent work on the interrelation of the lipids in hyperthyroidism and hypothyroidism is that of Foldes and Murphy (1946) In general they confirmed Mason's observations and extended them to include other lipids Thus plasma cholesterol cholesterol esters and phospholipids were found to be significantly increased in hypothyroidism The cholesterol esters/total cholesterol and total cholesterol/lipid phosphorus ratios were significantly increased In hyperthyroidism these changes were not so constant or significant The plasma phospholipids were decreased significantly, cholesterol and cholesterol esters were decreased absolutely

This study has adopted Means' principle in assessing thyroid function namely the use of multiple tests of which the following were employed basal metabolic rate radioactive iodine urinary excretion and serum lipid constituents including serum cholesterol (total and esters) serum lipid phosphorus total cholesterol/lipid phosphorus ratio and cholesterol esters/total cholesterol ratio (discussed in Chapter VIII) The use of the lipids as an index of thyroid activity is open to question for it is not known whether the changes in serum lipids are solely characteristic of individuals prone to coronary heart disease or whether they are in part the result of change in thyroid function For these reasons less reliance was placed on the serum lipids than on the basal metabolic rate and radioactive iodine excretion

Basal metabolic rate

The basal metabolic rate was obtained in 87 coronary patients on the morning after admission to the hospital Thus all rates were determined under the most favorable conditions using standardized procedure in the metabolic laboratory at the Massachusetts General Hospital

Table 5 shows the percentages by which the basal metabolic rates of the 87 patients varied from a standard mean

The mean basal metabolic rate in the coronary heart disease group is certainly shown to vary on the low side of accepted normal

TABLE VII-5 Percentage of variation from standard mean basal metabolic rate in coronary heart disease group of 87 males*

<i>Percentage of variation</i>	<i>No of patients</i>
—30 to —26	4
—25 to —21	11
—20 to —16	14
—15 to —11	20
—10 to — 6	17
— 5 to — 1	14
+ 1 to + 5	4
+ 6 to + 10	2
+ 11 to + 15	1
Mean \pm standard error	-12 ± 9
Range	—30 to +12

In 10 males and 3 females the basal metabolic rate record was unsatisfactory or incomplete

values for the general population. It is possible for a low metabolic rate to result from (a) depressed secretion of the thyroid gland (thyroxin) (b) depressed secretion of thyrotropic or other endocrine hormones or (c) failure of the end organs in either the body or the thyroid to respond to thyroxin or to thyrotropic hormone respectively. It must be considered however whether the low values recorded for the coronary group actually reflect a low metabolic rate or are the result of the method of calculation. The basal metabolic rate—the amount of energy expended under basal conditions—is expressed in terms of body heat as measured by oxygen consumption in relation to time and to surface area. The standards of oxygen consumption against which individual rates are measured have been determined empirically taking into account the variables of age, sex, and surface area in a limited number of normal persons. Of these variables the major one is surface area to which there are several theoretical objections. Since surface area is computed from height and weight there is bound to be some error especially in the shortest and tallest individuals whose weight is often out of proportion to their height. This fact has a bearing on our data for in the coronary heart disease group height was significantly less and lateral measurements were greater than in the general population (see Chapter IV) resulting in weight disproportionate to height. We believe therefore that the variation

of — 12 per cent from the standard basal metabolic rate shown by these patients may be normal for their type of physique

The coefficients of correlation between basal metabolic rate and variables such as uric acid urinary 17 ketosteroids, and various lipids ranged from + 09 to + 19 none were statistically significant The coefficients of correlation between basal metabolic rate and age and weight were — 10 and — 16 respectively, also not significant

Radioactive iodine

As stated previously the uptake of administered radioactive iodine measures the avidity of the thyroid gland for iodine Hertz Roberts and Evans (1938) showed that labeled iodine is concentrated by the thyroid in amounts many times greater than by any other tissue of the body This principle has been extended to the study of abnormal thyroid physiology and, specifically to the hyperthyroid and hypothyroid states

Essentially the technique adopted in the Massachusetts General Hospital and employed in the study of 21 of our patients is as follows The patient is given 100 cc of a solution containing 100 microcuries of radioactive iodine 131 (half life 8 days) and 100 micrograms of sodium iodide (as a carrier) A small aliquot is taken as a standard Urine is then collected for 48 hours Usually two 24 hour specimens are obtained however we have collected the specimens for 48 hours in two 6 hour specimens one 12 hour specimen and one 24 hour specimen

The three extreme ranges of thyroid function are given as follows (Rawson et al, 1949)

- 1 Euthyroid 53–84 per cent excretion in 48 hours
- 2 Thyrotoxic 8–32 per cent excretion in 48 hours
- 3 Myxedematous 74–93 per cent excretion in 48 hours

Radioactive iodine excretion by the 21 coronary patients revealed a slight downward change from the euthyroid state (see Figure 2) The percentage of radioactive iodine excreted in the urine in 48 hours ranged from 47 to 80 with an average of 60 While it is known that this test is not as critical in evaluating the thyroid status as an analysis of the blood iodine levels it is nevertheless satisfactory and informative for the purpose of the present study

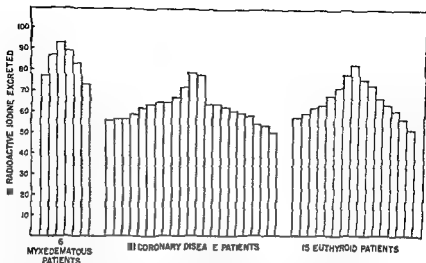


FIGURE VII-2 Per cent of radioactive iodine excreted in the urine in 48 hours by 6 myxedematous patients 21 coronary heart disease patients and 15 euthyroid patients. The coronary patients showed a pattern similar to that of the euthyroid patients. Both these groups showed lower radioactive iodine excretion than the myxedematous group (Modeled after Rawson et al.)

Serum lipid constituents

The study of serum cholesterol (free esters and total) serum lipid phosphorus and total cholesterol/lipid phosphorus ratio substantiates the evidence of the low basal metabolic rate that there is a slight change from the euthyroid state in coronary heart disease toward the hypothyroid state.

The average serum total cholesterol in coronary heart disease in our series was 286 mg per cent serum cholesterol esters were 177 mg per cent and serum lipid phosphorus was 12.6 mg per cent. While these values are significantly lower than the values reported in known hypothyroid states by Foldes and Murphy (1946) they are significantly higher than normal values (see Chapter VIII). The total cholesterol/lipid phosphorus ratio is significantly higher in the hypothyroid state than in the euthyroid state. In this respect the coronary heart disease group was again intermediate between euthyroidism and hypothyroidism.

It is interesting that the three factors—serum total cholesterol, serum lipid phosphorus, and total cholesterol/lipid phosphorus ratio—are increased in both the hypothyroid and the coronary heart

disease states. The essential difference is the degree of increase. In hypothyroidism the serum total cholesterol rises to inordinately high levels while the serum lipid phosphorus does not rise proportionately a fact which accounts for the high total cholesterol/lipid phosphorus ratio. In coronary heart disease, the serum cholesterol is moderately increased and the serum lipid phosphorus is slightly increased resulting in a moderate elevation of the total cholesterol/lipid phosphorus ratio.

It is of further interest that there was no significant correlation between basal metabolic rate and serum total cholesterol. This fact could be interpreted as meaning that serum total cholesterol and basal metabolic rate are independent variables in the presence of the serum lipid abnormalities in coronary heart disease. In hypothyroidism there is a high negative correlation between basal metabolic rate and serum total cholesterol.

The rise and fall of serum total cholesterol in hypothyroidism and hyperthyroidism respectively suggest that there is an inverse relationship between serum total cholesterol and oxygen consumption (Epstein and Lande 1922). In such conditions as Addison's disease and starvation when oxygen consumption is low however it is found that, contrary to expectation low values of cholesterol are found in the serum. Cutting et al (1934) showed that in normal individuals while dinitrophenol raised the basal metabolism (oxygen consumption), it did not affect the serum total cholesterol.

Interpretation of 17 Ketosteroid and Thyroid Studies

Since coronary heart disease is predominantly a male disease, and since ketosteroids are a crude estimate of androgenic activity it was thought that the coronary heart disease group might show an increased urinary sterone excretion. On the other hand since coronary heart disease is sometimes considered a chronic disease in the sense that once an individual has experienced it he is advised to curtail his usual activities it would not have been surprising to find a lower 17 ketosteroid excretion.

The results of the study suggest a decrease in urinary sterone excretion in the coronary group. It is noteworthy that the sterone excretion was decreased to a greater degree in those who died from coronary heart disease. This observation raises two questions. (a) Would a periodic follow up of the urinary sterone excretion be

worth while in the coronary group? (b) If during a follow up study the sterone excretion decreased would it benefit the patient to reverse this trend by androgen replacement therapy? Further study is needed on these points

The study of basal metabolic rate indicated that it may not provide a basis for definite evaluation of the thyroid status of the coronary group. The rate is lower than that considered normal, but it has been shown that this apparent deviation may be in large part associated with the physique of the patients rather than with any decrease in oxygen consumption due to disease. The study of urinary radioactive iodine excretion interrelations of the lipids and coefficients of correlation between various factors however suggests that there is some degree of functional alteration in the thyroid gland in the direction of hypothyroidism. The bearing of this alteration on the genesis of coronary heart disease is not immediately apparent but in view of the known virtual absence of the disease in hyperthyroid states it is reasonable to suggest that the thyroid probably plays a role albeit minor in the genesis of the disease.

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CHAPTER VIII

Biochemical Findings The Interrelations of Serum Lipids

HISTORIANS claim that Pouletier de la Salle circa 1769 first called attention to a substance in gallstones that is soluble in alcohol and that forms crystals upon evaporation (Bills 1935) Chevreul in 1824 repeated these experiments and named the substance cholesterol (*chole* bile *steros* solid) Denis (1830) is credited with being the first to report that blood serum contains cholesterol

Although the chemical formula of cholesterol $C_{27}H_{46}O$ was suggested by Reimtzter in 1888 the molecular structure has been a subject of controversy for many years (Schoenheimer 1926) However through the efforts of many investigators the structure has been accepted subject to change as a phenanthrene cyclopentane or cholane form of sterol ring

Possibly the earliest association between cholesterol and atherosclerosis was Vogel's observation in 1847 that cholesterol is present in atherosclerotic lesions Windaus analyzed various diseased aortae in 1910 and reported six times as much cholesterol and twenty times as much cholesterol ester in atherosclerotic aortae as were observed in normal aortae Schoenheimer (1928 1934) and others extended these observations and concluded after performing chemical analyses of many aortae that the proportion of lipids in the aorta increases with age and atherosclerosis

From these observations investigators both clinical and experimental almost concurrently began to study the interdependence of the level of serum cholesterol and the degree of atherosclerosis Experimentalists led by Anitschkow and Chalutow (1913) produced atherosclerosis in the rabbit by feeding the animal large quantities of cholesterol Clinicians attempted to learn whether the incidence of atherosclerosis in the population with hypercholesterolemia was higher than in the normal population Thus indi

viduals with hereditary hypercholesterolemia (Boas et al 1948), nephrosis (Bloor, 1917), hypothyroidism (Epstein and Lande, 1922) xanthomatosis (Thannhauser, 1940) and diabetes mellitus (Rabinowitch 1935 Joslin et al 1917) were studied in order to ascertain the incidence of atherosclerosis

Both methods of approach have had their strong opponents and proponents Duff (1935) objected to Anitschkow's conclusions on the grounds that cholesterol an animal sterol may have an effect as an unnatural factor in an herbivorous diet that it would not necessarily have in the diet of human beings which commonly includes animal sterols Leary (1949) on the other hand disagreed with Duff and came to the same conclusions as Anitschkow after repeating and confirming Anitschkow's experiments and after studying human autopsy material with a polarizing microscope

There is no satisfactory evidence that entirely confirms or denies a causal relation between the state of hypercholesterolemia and atherosclerosis Lande and Sperry (1936) maintained from their clinical analysis of human autopsy material that no relation exists between hypercholesterolemia and atherosclerosis The association between hypercholesterolemia and cardiovascular diseases has been denied by several investigators (Page Kirk and Van Slyke 1936 Elliot and Nuzum 1936) However the bulk of the evidence is in favor of an association (Mjassnikow 1926 Davis Stern and Lesnick, 1937 Barker 1939 Poundexter and Bruger 1938 Morrison et al 1948 Steiner, 1948) Nevertheless the evidence for the existence of a higher incidence of atherosclerosis in individuals who have diseases that manifest a hypercholesterolemia cannot be accepted as concrete evidence of a causal relation, there is the possibility that atherosclerosis and hypercholesterolemia are both the end products of an altered metabolic state This possibility is further strengthened by Lerman and White's observations (1946) that in those who have experienced myocardial infarction prior to the age of 40 the serum cholesterol is higher and the basal metabolic rates are lower than in suitable controls Steiner and Kendall (1946) extended this finding and experimentally produced atherosclerosis in dogs by the addition of thiouracil and cholesterol to their usual diet Steiner's work confirmed Shapiro's observations that thyroidectomy and other alterations of the glandular state favor the development of atherosclerosis (Shapiro 1927) Thus

it is reasonable to suggest that atherosclerosis may be the end result of the combination of altered biochemical and hormonal metabolism probably caused by a local vascular fault or strain and not necessarily the result of any one factor such as an elevated serum cholesterol. Blumgart (1950) has found upon examination of human cases of long standing hypothyroidism (created by subtotal thyroidectomy in 1933) that the degree of atherosclerosis is not significantly greater than is usually obtained for those in the same age group. This observation causes one to question the clinical belief that hypothyroidism predisposes to atherosclerosis. However, Blumgart's particular cases perhaps have not lived long enough to develop atherosclerosis in spite of hypothyroidism. In addition, Blumgart's cases usually receive some thyroid medication which may in itself be protective against atherosclerosis.

Lipid Values

In the present study in addition to the determination of the absolute level of serum total cholesterol in the coronary heart disease group and a matched control group of healthy men, the question of the influence on the level of serum total cholesterol of such factors as age, weight, body build, and diet was considered and interpreted with particular reference to the range of the normal level and its etiologic relation to coronary heart disease. Since cholesterol has been shown to be only one of the variables concerned in the etiology of coronary heart disease, other lipids such as phospholipids were also determined in both groups. Furthermore, the interrelations of the various lipids were also considered because of the current viewpoint that the colloidal state of all the substances within the serum is more important than any one individual substance.

The blood samples were drawn at any time during the day, not only for expediency but also because fasting specimens offer no particular advantage insofar as accuracy is concerned (Bruger and Somach, 1932; Turner and Steiner, 1939). The Bloor methods (Bloor, 1917; Bloor and Knudson, 1916) for determining total cholesterol and cholesterol esters were employed throughout the study. In this laboratory Miss Margaret Rourke found that they give as accurate, dependable, and comparable results as the Schoenheimer-Sperry technique (1934). Serum phospholipids were

TABLE VIII-1 Serum cholesterol (free esters and total) and phospholipids (lecithin*) in coronary heart disease group and matched control group each of 97 males

	CORONARY GROUP			CONTROL GROUP		
	No of cases	Range mg %	Mean \pm S.E. mg %	No of cases	Range mg %	Mean \pm S.E. mg %
Free cholesterol	94†	37-227	110.43 \pm 3.9	97	45-216	100.9 \pm 3.9
Cholesterol esters	94	88-376	176.6 \pm 5.5	97	70-260	141.0 \pm 3.9
Total cholesterol	97	167-490	286.5 \pm 6.6	97	155-455	241.9 \pm 5.5
Phospholipids (lecithin)	61	177-414	316.4 \pm 6.7	90	221-397	305.7 \pm 4.2

*Lecithin which comprises about 80 per cent of the phospholipids is estimated by multiplying the value of the determined lipid phosphorus by a factor of 25

†Whenever the number in either group for any variable is less than 97 it shows a loss in determinations due to (a) laboratory waste or (b) having started late in the study to determine this variable

determined by the Fiske and Subbarow technique (1925) In our determinations lecithin was expressed as 25 times the lipid phosphorus value (lipid phosphorus is the amount of phosphorus in the total lipids of the serum)

The range and the values assumed by the mean of the four serum lipids (cholesterol—free esters and total—and lipid phosphorus) in the coronary heart disease group and in the 97 matched controls are listed in Table 1 * The average serum levels of cholesterol esters and total cholesterol were greater to a highly significant degree in the coronary heart disease group than in the matched control group While the average serum levels of phospholipids and free cholesterol were higher in the coronary heart disease group as compared with the matched control group the difference did not attain significance

The distributions of the two groups for serum total cholesterol are plotted in Figure 1 The degree of overlap is apparent in spite of the significant difference in the means It is obvious that within the coronary heart disease population there were many individuals whose value of serum total cholesterol equaled that found within the healthy matched control group Furthermore the extent of the variation hardly ever exceeded one standard deviation in either

*Although the patients and controls were matched for various factors such as age weight height occupation and ethnic origin the matching did not extend to serum phospholipids and serum cholesterol (free esters and total) values Consequently in respect to these values the differences between the two groups are significant in the same way as for any unmatched groups

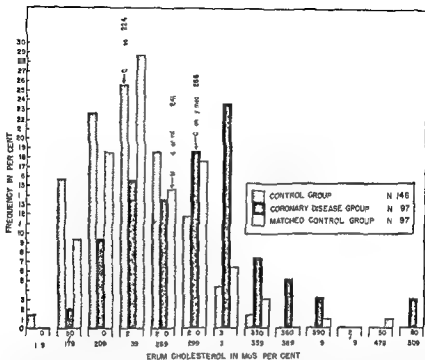


FIGURE VIII-1 Level of serum total cholesterol in coronary heart disease group unmatched control group and matched control group. The distributions within the histogram are not discontinuous however there were more individuals with coronary heart disease whose cholesterol exceeded 300 mg per cent, while there were more in the control groups whose serum cholesterol was less than 210 mg per cent.

direction as the following data show. It was calculated that 15 per cent of the matched control group (22 individuals) exceeded the mean value of serum total cholesterol (286 mg per cent) of the coronary heart disease group. However only 2 individuals in the matched control group had a serum total cholesterol greater than 352 mg per cent (the average of the coronary group plus one standard deviation). Conversely 27 members of the coronary group had a serum total cholesterol below the mean value of the matched control group (241 mg per cent). But only 2 coronary patients had a serum cholesterol below 181 mg per cent (the mean value minus one standard deviation of the matched control group).

As in the case of the serum total cholesterol there is considerable overlap of the ranges of the two groups for cholesterol esters

It was calculated from the data that 20 per cent of the matched control group (29 individuals) exceeded the mean value of serum cholesterol esters (177 mg per cent) of the coronary group. However only 2 individuals in the matched control group exceeded the value of the mean plus one standard deviation (230 mg per cent) of the coronary group.

Age Changes and Serum Cholesterol

It is generally conceded that serum total cholesterol, cholesterol esters and free cholesterol are lower in infants than in adults, however the change in these variables from infancy to maturity is a disputed subject. Several studies have concluded that there is probably a rise in serum total cholesterol level after puberty in the male (Parhon and Parhon 1923a Ward 1931) while other reports have claimed that there is no such relation (Blix 1926, Foldes and Murphy 1946). Before puberty however the serum total cholesterol level seems to be lower than in adult life (Boyd 1936) and the evidence appears to support Sperry (1936) who asserts that the level is lowest during the neonatal period in (full term) infants and approximates adult levels in late prepuberty and early puberty (Sperry 1936 Offenkrantz and Karshan 1936). Page has concluded that no comparable rise exists postpuberally (Page et al 1935 Hodges et al 1943). Our calculation from his data however is not consonant with his conclusion (Gertler, Garn and Bland 1950) and Keys et al (1950) have recently confirmed our results. Data for ages above 65 have recently been presented (Gertler and Oppenheimer 1953).

Sampling errors, technique variations and so on may account for some of the discrepancies. Several studies (Foldes and Murphy, 1946) were conducted on groups too small to yield results that were statistically significant. Also individuals hospitalized for disorders presumably not related to cholesterol metabolism were included in some of the so called normals (Foldes and Murphy 1946) although no evidence has yet been offered that systematic errors do not appear in such procedures. Furthermore the influences of race, diet, occupation and socio-economic status though discussed in theory (Wilber and Levine 1949 Boas and Adlersberg 1945 Corcoran and Rabinowitch 1937) have not in general been considered in previous studies.

TABLE VIII-2 Serum total cholesterol in coronary heart disease group of 97 males by age decades

Age	No of cases	Range mg %	Mean \pm S.E. mg %
20-29	7	194-400	245.0 \pm 27
30-39	53	167-490	286.0 \pm 9
40-49	35	208-490	301.0 \pm 11
50-59	2	218-301	259

The evidence from the present study concerning the change in the level of serum total cholesterol with age is not quite clear (Tables 2 and 3). While the marked upward trend of cholesterol with age is close to significance for the coronary heart disease group the slight rise for the matched control group is certainly not significant. It will be noted that the elevation of the serum total cholesterol for the coronary heart disease group over the matched control group discussed above (see also Table 1) is apparent at each age level.

For the series of 146 unmatched controls the mean showed a rather marked rise from 195 mg per cent in the 20-29 year age group to 254 mg per cent in the 50-59 year age group a trend that is highly significant (Gertler, Garn and Bland 1950).

If there is a rise in serum total cholesterol with age it may be suggested by these data that the clinician must consider the factor of age if he is to derive much meaning from a patient's level of serum total cholesterol. In addition as will be shown below under the heading of Physique and Serum Cholesterol the factor of physique must be considered.

There is some evidence that beyond the sixth decade of life no further elevation of cholesterol occurs (Keys et al 1950) there may even be a drop in cholesterol level after this time (Gertler, Garn and Bland 1950; Gertler and Oppenheimer 1953). While

TABLE VIII-3 Serum total cholesterol in matched control group of 94 males by age decades

Age	No of cases	Range mg %	Mean \pm S.E. mg %
20-29	7	167-425	230.0 \pm 12
30-39	53	155-455	227.0 \pm 5
40-49	32	175-350	246.0 \pm 8
50-59	2	214-270	242

No data were recorded for 3 controls in this age group

TABLE VIII-4 Serum total cholesterol levels in those of Jewish origin and of non Jewish origin in coronary heart disease group and unmatched control group

	ENTIRE GROUP		JEWS		NON JEWS	
	No of cases	Mean age	No of cases	Cholesterol mean \pm S.E. mg %	No of cases	Cholesterol mean \pm S.E. mg %
Coronary group	97	38.5	27	281.76 \pm 14.54	70	288.75 \pm 7.50
Control group	97	38.4	27	256.96 \pm 12.54	70	236.67 \pm 5.61

this has been interpreted by some as evidence of 'debility' in age it is possible that it is a statistical or selective phenomenon due to the differential mortality of low cholesterol and high cholesterol individuals. Thus if elevated cholesterol is associated with decreased life span the longer lived individuals in an older group will be simply the low-cholesterol surviving population. The data though scanty may point to basic factors in human survival (Dublin 1948).

Race and Serum Cholesterol

There are unconfirmed claims that atherosclerosis is practically unknown among peoples like the Chinese, Eskimos and Okinawans whose diet is purported to contain very little cholesterol and whose serum total cholesterol is said to be lower than that of the American population. However a survey made by the Coronary Research Laboratory did not substantiate any relation between ingested cholesterol and the level of serum total cholesterol (see Chapter X).

It is apparent that coronary heart disease occurred in our study with greater frequency in individuals who might be classified as the mid-Mediterranean ethnic group. We did not investigate this question completely but we did analyze the findings in two groups of individuals: the Jewish and Italian. Since individuals of Jewish origin were numerous in the series the levels of serum total cholesterol were determined both for them and for the non-Jewish population of the coronary heart disease group and the matched control group. The results are summarized in Table 4.

In the coronary heart disease group there was a small and not statistically significant difference in the level of serum total cholesterol between the Jews and non-Jews. In the matched control group

the difference was somewhat larger but in the opposite direction and also not statistically significant. Although the cholesterol levels in the Jews of the coronary heart disease group exceeded those of the matched control Jews the difference was not statistically significant but between the non Jewish coronary and control groups there was a significant difference.

The 6 Italians in the coronary heart disease group were compared in a similar way with the 6 Italians in the matched control group. The average serum total cholesterol for those with coronary heart disease was 278.15 mg per cent while for the 6 in the matched control group it was 253.0 mg per cent. In a group so small this cannot be said to be a significant difference.

Lipid Indices

The ratios for total cholesterol/lipid phosphorus, cholesterol esters/total cholesterol and free cholesterol/cholesterol esters are summarized in Table 5.

It has been stated that the deposition of cholesterol and its esters does not necessarily imply the existence of hypercholesterolemia. The ability of cholesterol to remain in solution in the blood requires a colloid stabilizer which will prevent its being precipitated and it has been postulated that the phospholipids act as such a stabilizer to a cholesterol suspension in vitro (Ahrens and Kunkel 1949; Thannhauser 1949). This is borne out by the fact that lecithin constituting about 80 per cent of the phospholipids is known to be antagonistic to cholesterol in certain biological and chemical reactions and hence probably would prevent deposition. It was

TABLE VIII-5 Values of lipid indices in coronary heart disease group and matched control group

	CORONARY GROUP			CONTROL GROUP		
	No of cases	Range mg %	Mean \pm S.E. mg %	No of cases	Range mg %	Mean \pm S.E. mg %
Total cholesterol	60*	14.5-33.0	27.4 \pm .51	90	12.9-48.7	19.4 \pm .33
lipid phosphorus						
Cholesterol esters	94	36.0-84.2	61.4 \pm 1.06	97	39.0-79.0	58.5 \pm .90
total cholesterol						
Free cholesterol	94	30.3-144.9	68.2 \pm 3.09	97	36.0-133.8	76.9 \pm 2.99
cholesterol esters						

*A number less than 97 indicates laboratory wastage etc.

suggested by Peters and Man however that it is not so much any individual lipid as the interrelation of all the lipids, their relative ratio that is important to stabilization of cholesterol. An experiment reported by Ladd et al (1949) showed that rabbits fed with cholesterol and Tween 80* did not in fact, develop atherosclerosis. The explanation given was that the serum phospholipids were increased to high levels and instituted a protective mechanism.

Cholesterol deposition may on the other hand, sometimes result from hypercholesterolemia. Popjak (1945) suggested that free cholesterol regulates the mobilization of fatty acids and the rate of phospholipid synthesis. Thus it may be reasoned that an excess of free cholesterol may decrease the blood phospholipids and that this in turn may lead to deposition of cholesterol.

The evidence accumulated by Ladd et al (1949), Browder (1915), Popjak (1945) and Ahrens and Kunkel (1949) are consonant with the findings in this study on serum lipids in the healthy control group and in the coronary heart disease group. There is as stated elsewhere considerable overlapping of the serum cholesterol in both groups (see Figure 1), without any indication of a threshold level of serum total cholesterol that is causally related to coronary heart disease.

The coefficients of correlation between serum cholesterol and serum phospholipids were determined + 51 and + 55 for the coronary heart disease group and the matched control group respectively. Both coefficients are highly significant demonstrating that total cholesterol and phospholipids are correlated to a high degree in both groups and strengthening the thesis that the interrelations of serum lipids are more important than either single lipid.

The correlation between serum total cholesterol and lipid phosphorus is practically unaffected by eliminating by a partial correlation technique any commonality or effect that age might have on each of the two variables. The scattergram depicting the relation between serum total cholesterol and lipid phosphorus for each group is given in Figure 2.

The relation of total cholesterol to lipid phosphorus normally is a constant one as demonstrated by Peters and Man (1943). Formulae for calculating lipid phosphorus when serum total cholesterol is known derived from our data are

Polyoxyethylene sorbitan mono-oleate

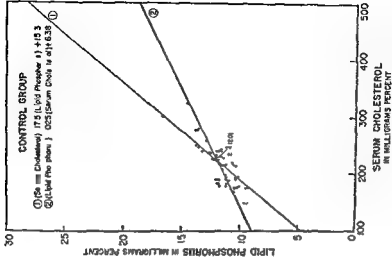
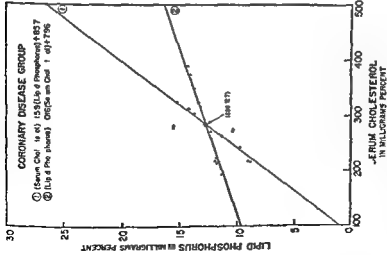


FIGURE VIII-2 Scattergrams with regression lines showing relation between serum (total cholesterol and serum lipid phosphorus in coronary heart disease group and unmatched control group. The coefficients of correlation between serum lipid phosphorus and serum cholesterol were $+ 51 \pm .09$ and $+ 66 \pm .05$ for the coronary group and the unmatched control group respectively.

Lipid phosphorus \approx 0.025 total cholesterol + 6.38 (matched control group)

Lipid phosphorus \approx 0.016 total cholesterol + 7.96 (coronary group)

The degree of mutability of the cholesterol/lipid phosphorus ratio may be obtained from Figure 3. It is evident that an elevation or depression of either total cholesterol or lipid phosphorus or both may not necessarily produce an abnormal cholesterol/lipid phosphorus ratio. The cholesterol/lipid phosphorus ratio will vary under a number of circumstances (see Table 6). It will be increased (a) when the serum lipid phosphorus is rising at its expected rate in the presence of serum total cholesterol that is rising faster than its expected rate (b) when the serum lipid phosphorus is rising slower than its expected rate in the presence of an expected rise or a faster than expected rise in the serum total cholesterol value.

Since the time at which the writing of this report was begun several important contributions have been made to the analysis of this problem. The first development came when John W. Gofman made it known that giant molecules (designated S_2 10-20) are found in excessive amounts in patients with atherosclerosis and in those who experience illnesses which are thought to be predisposing to atherosclerosis. These findings have been confirmed by several groups. Additional research done by David P. Barr and his associates disclosed the fact that patients who have survived coronary occlusion exhibit a reduction of albumin and alpha lipoprotein and a relative and absolute increase in beta lipoprotein. While these two new findings are provocative from the evidence presented it has not been shown that they are able to assist in pre-selecting the coronary prone individual to any greater degree than is the total cholesterol/lipid phosphorus ratio.

Physique and Serum Cholesterol

Determination of the differences between the levels of the various lipids for the various dominant physiques is imperative not only to establish the meaning of normal lipid levels but also to determine the difference if any that exists between (a) the physiques within any one group and (b) similar physiques in any two groups. Since the physical constitution is predetermined to a large degree it is reasonable to suppose, without postulating any degree of association or

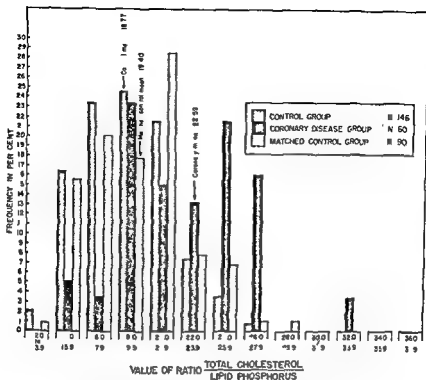


FIGURE VIII-3 Frequency distribution of total cholesterol/lipid phosphorus in coronary heart disease group unmatched control group and matched control group. The mean value of the ratio was significantly greater in the coronary group than in either of the other two groups.

TABLE VIII-6 Effect of various combinations of serum cholesterol and serum lipid phosphorus values on cholesterol/lipid phosphorus ratio

Serum cholesterol	Serum lipid phosphorus	Chol/lipid phosphorus ratio
elevated	normal	elevated
elevated	elevated	need not be elevated
elevated	decreased	elevated
normal	normal	unchanged
normal	elevated	decreased
normal	decreased	elevated
decreased	normal	decreased
decreased	elevated	decreased
decreased	decreased	need not be decreased

causal relation that the chemical attributes such as serum cholesterol and serum uric acid likewise may be genetically determined. Hence an attempt to associate physique with serum lipids has certain theoretical justification.

This has been done in the past in studies that correlate the lipid levels with various physiques (Gildea et al, 1936; McQuarrie et al, 1933; Mjassnikow, 1927). The reliability of these studies is necessarily limited by their haphazard system of physique classification and their ill defined terminology (see Chapter IV). Some observers have used the terms obese and lean (Bruger and Poindexter, 1934). Others presented a tripolar system with definite poles—obese, medium and lean (Labbe and Heitz, 1924). Still others have followed Kretschmer's terminology (1925) but not his anthropometry with a tripolar classification of pyknic, intermediate and leptosomatic (Gildea et al, 1936). At best, the systems are not strictly comparable, at worst the individual variations in standards curtail the accuracy of the interpretations and make comparative ratings difficult. However, it is important to emphasize the fact that despite these drawbacks, consistent and meaningful conclusions have emerged. As described in Chapter IV, in order to avoid as far as possible the limitations described above without placing undue stress on ratios or index scales of build, the Sheldonian system of body build rating has been selected for use in this work (Sheldon et al, 1940).

The first indication that a differential relation exists between the various lipids and the physiques for both the coronary and the unmatched control groups was shown by the coefficients of correlation which ranged from -0.21 to $+0.23$. While a few of these coefficients reached the level of significance, they were so small that they did not contribute anything to our understanding of any basic trends. Some of the more pertinent correlations are (a) between phospholipids and ponderal index (-0.15 ± 0.13 and -0.21 ± 0.08 for the coronary heart disease group and the control group respectively) and (b) between serum total cholesterol and ponderal index (-0.11 ± 0.10 and -0.13 ± 0.08 for the coronary heart disease group and the control group respectively).

In Table 7 the values of the four lipids—free cholesterol, cholesterol esters, total cholesterol and phospholipids—are listed under physical groups which have been classified into primary domi-

TABLE VIII-7 Serum lipids by physques in coronary heart disease group of 97 males* and unmatched control group of 146 males (Mean \pm S.E. mg %)

Physique	No of cases	Free cholesterol	No of cases	Cholesterol esters	No of cases	Total cholesterol	No of cases	Phospho lipid†
ENDOMORPHIC								
coronary control difference	24 51	113.51 \pm 9.4 101.51 \pm 4.1 ns	24 51	176.0 \pm 11.7 133.1 \pm 4.8 ‡	25 51	286.8 \pm 12.9 234.6 \pm 6.6 ‡	19 51	310.6 \pm 11.7 311.3 \pm 5.8 ns
MESOMORPHIC								
coronary control difference	43 34	110.2 \pm 5.1 104.3 \pm 4.4 ns	43 34	184.2 \pm 7.0 119.0 \pm 4.1 ‡	43 34	294.4 \pm 9.3 223.3 \pm 6.2 ‡	27 34	319.5 \pm 10.5 300.3 \pm 6.0 ns
ECTOMORPHIC								
coronary control difference	9 34	100.4 \pm 11.5 96.8 \pm 4.6 ns	9 34	164.1 \pm 16.4 111.0 \pm 4.4 §	9 34	264.6 \pm 19.8 207.8 \pm 6.0 ‡	5 34	328.0 \pm 12.0 281.2 \pm 6.4 ‡
MID-RANGE								
coronary control difference	18 27	111.6 \pm 19.0 94.0 \pm 5.6 ns	18 27	165.8 \pm 15.2 133.4 \pm 6.3 §	20 27	279.1 \pm 16.3 227.4 \pm 8.2 ‡	11 27	314.0 \pm 19.0 298.3 \pm 7.5 ns
TOTAL								
coronary control difference	94 146	110.4 \pm 3.9 99.7 \pm 2.3 §	94 146	176.7 \pm 5.5 124.7 \pm 2.6 ‡	97 146	286.5 \pm 6.6 244.4 \pm 3.5 ‡	61 146	316.4 \pm 6.7 299.3 \pm 3.3 §

*In 3 cases free cholesterol and cholesterol esters were not determined. In 36 cases lipid phosphorus (phospholipid) determinations were not made.

†Phospholipids are expressed as 25 times the lipid phosphorus.

‡Significant at the 1 per cent level.

§Significant at the 5 per cent level.

NS—Not significant.

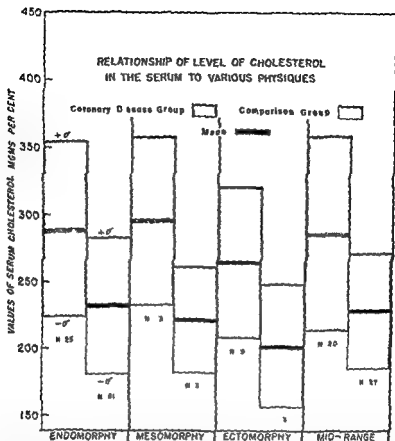


FIGURE VII-4 Serum total cholesterol levels in coronary heart disease group and unmatched control group. Within the coronary group the mesomorphs had a higher level of serum total cholesterol than the endomorphs or ectomorphs. Within the control group endomorphs had a higher level of serum total cholesterol than mesomorphs or ectomorphs. A comparison of the coronary with the control group shows higher levels in the coronary group for all physiques the largest difference occurring in the category of mesomorphy.

nances for the coronary and unmatched control groups. Comparisons were also made between the means of the four major physical categories both within and between the matched control group and the coronary heart disease group (See also Figure 4.)

In evaluating the relation of morphological characteristics to the level of serum total cholesterol it should be kept in mind that in an average population the levels in endomorphs, mesomorphs and mid range individuals exceed the level in the ectomorphs. At the age of 35 the mean levels of serum total cholesterol for the

ectomorphs and for the other groups combined would be 207 mg per cent and 224 mg per cent respectively. Abnormal levels would assume the values of 207 ± 74 mg per cent and 224 ± 82 mg per cent while high but not abnormal levels would assume values of $207 + 37$ mg per cent and $224 + 41$ mg per cent (Gertler, Garn and Bland 1950).

The further interrelation of age and morphological characteristics with the level of serum total cholesterol is now apparent. While these figures do not include enough individuals for a complete age morphological survey, it is reasonable to suggest that an ectomorph at any age would possess on the average a lower level of serum cholesterol than would individuals with other physiques (see Figure 4). The assessment of age corrections and physical corrections is important before any inference is made concerning the level of a determined serum total cholesterol.

Conclusions

A coronary threshold of cholesterol does not appear to exist if such a threshold had to be reached before coronary heart disease manifested itself; the differences between physiques would be wiped out and endomorphs, mesomorphs, ectomorphs, and mid range individuals would all conform to this threshold. The fact that such a condition does not exist confirms the findings of this study, namely that coronary heart disease can and does exist well below the accepted limits of hypercholesterolemia, although hypercholesterolemia is undoubtedly an association of coronary heart disease among the patients as a group.

If then absolute serum cholesterol values are not the answer, what explains the constantly higher lipid levels in the coronary heart disease patients, physique by physique, and at the same time the continued maintenance of differences between physiques within the two groups?

The answer to both questions comes in part from an examination of the magnitude of the differences in Table 7 and Figure 4. For all lipids, the differences between the coronary and unmatched control endomorphs, the coronary and unmatched control ectomorphs, and the coronary and unmatched control mesomorphs are of the same order of magnitude. This suggests strongly the same conclusion that we have previously considered, namely that in

coronary heart disease there is a specific predisposition to the disease in addition to any disturbance in lipid metabolism. Since the predisposition to the disease may further augment the lipid levels many workers have decided that it is the absolute lipid level that is important. However, the evidence here suggests that a high absolute lipid level is important only in that it may reveal the presence of the predisposition to coronary heart disease that is hypercholesterolemia of familial type but that with constitutionally low cholesterol levels the predisposition factor is hidden. Thus coronary heart disease is found in individuals with low lipid levels because it is the predisposition constant that is important not the absolute level.

The predisposition factor need not arise primarily from a difference in serum lipids but may be due to several independent additional factors. One factor might be the yet unproven concept of the difference in the thickness and permeability of the coronary arteries between mesomorphs and the other physiques. Thus it may be that the muscular layer of the patients with coronary heart disease (particularly the mesomorphs) is thicker thereby producing a narrower lumen which is more easily obliterated by equal amounts of plaque formation. Or one may postulate the theory that between the coronary heart disease patients and the control patients there is a difference in the permeability of the coronary intimal tissue which will permit an easier penetration by the cholesterol or macrophages in the coronary intima.

Cholesterol by itself is doubtless an important etiological agent in coronary heart disease but it is to be emphasized that it is only one of the links in the chain which includes such endocrine factors as the thyroid and adrenal thickening of arterial wall intima, colloid stability, which is partially controlled by the lipid phosphorus and rates of anabolism and catabolism of cholesterol within the arterial walls. Moreover vitamins such as pantothenic acid and ascorbic acid have recently been shown to influence the metabolism of cholesterol.

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CHAPTER IX

Biochemical Findings The Role of Serum Uric Acid

URIC acid is the principal end product of the catabolism of the purine and pyrimidine bases in man (Peters and Van Slyke 1946). Uric acid may be synthesized from the various constituents of the metabolic pool as Shemin and Rittenberg (1947) have demonstrated in that the amino acid glycine is incorporated into uric acid. The bulk of the evidence (Minkowski 1886 Schoenheimer 1942) suggests that this synthesis takes place in the liver.

Clinical Observations

The association between an abnormal uric acid metabolism and gout dates back to 1797 when Wollaston demonstrated that the deposits surrounding gouty joints are composed of uric acid to a large degree. Garrod in 1848 was probably the first to suggest a causal relation between gout and an increased content of uric acid in the blood. Since Garrod's observations there has accumulated a voluminous literature which confirms (Jordan and Gaston 1932 Jacobson 1938) and modifies (Schnitzer and Richter 1936 Adlersberg et al 1942) his viewpoint.

Hyperuricemia may exist as a result of renal failure (Bröchner Mortensen 1938) increased cellular breakdown (Isaacs 1923) or gout. In reviewing many factors associated with gout one finds that it is primarily an adult male disease; prepubertal and adolescent females and males are practically spared (Scudamore 1823). Bauer and Klemperer (1947) state that slightly over 95 per cent of all patients afflicted with gout are males. Persons of large frame and vigorous appetite with a tendency to corpulence may be said to have a natural proclivity to gout (Roberts 1900). Scudamore reported from a study of 515 cases of gout that his youngest case was eight years old. Thirteen cases appeared in the first two decades of life and the majority of his remaining cases occurred in men of

the fifth sixth and seventh decades of life. These factors of male prevalence, large frame and age distribution along with familial tendency (Smyth et al 1948) are common to both coronary heart disease and the gouty diathesis (Huchard 1899).

A causal relation between the gouty diathesis and arteriosclerosis has been a clinical concept at least since the early part of this century. Roberts observed clinically in patients with gout the syndrome of the runaway heart in which the palpitations were severe and necessitated rest on the part of the patient. Occasionally angina pectoris and other chest pains simulating angina pectoris are associated with gout. In addition Roberts stated that 'gouty persons exhibit a marked proclivity to the formation of such clots [thrombi causing thrombophlebitis] in the veins of the lower extremities'. Similar accurate clinical observations were made by Huchard (1899) who said

The influence of gouty diathesis on the development of arteriosclerosis and arterial atheroma has been well established and it would appear ineffectual to dwell upon this. *Gout is to the arteries what rheumatism is to the heart* and this is why presence of arterial degeneration appears to a greater degree in certain families of hereditary gout. Accordingly arteriosclerosis and vascular atheromata are to be found in certain subjects as the only manifestation of this diathesis. Thus one sees in those of familial gout, the slow development of arteriosclerotic lesions concomitantly with joint symptoms.

It was such a clinical suggestion of an association between gout and coronary heart disease that led to the study of the content of uric acid in the serum of the young coronary patient. In addition, the problems were undertaken of (a) establishing normal values for the content of uric acid in the serum (b) studying the effect of differences of physique and (c) considering the influence of age on the serum uric acid content.

The serum uric acid values for 92 men with coronary heart disease and 96 matched controls are given in Figure 1 and Table 1. The average level of serum uric acid in the coronary heart disease group was significantly higher than that of the matched control group. Forty eight per cent of the coronary patients had levels of 5.0 mg per cent or over compared with 41 per cent of the matched controls. At levels of 6.0 mg per cent or over the difference was much greater 22 per cent of the coronary group as against 6 per cent of the matched controls. The interpretation of the higher levels

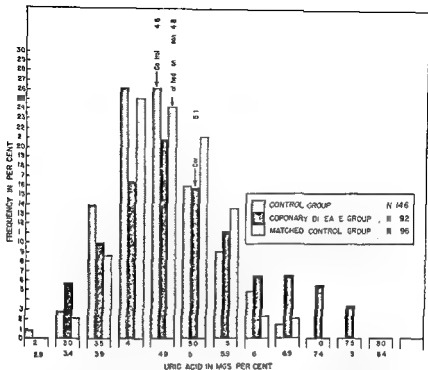


FIGURE IX-1 Frequency distribution of uric acid in coronary heart disease group unmatched control group and matched control group. It is to be noted that 22 per cent of the individuals within the coronary group had serum uric acid values greater than 6.0 mg per cent while only 6 per cent of the unmatched or matched control groups had serum uric acid values greater than 6.0 mg per cent.

TABLE IX-1 Serum uric acid levels* in coronary heart disease group of 92 males† and matched control group of 96 males†

Level mg %	Coronary group	Control group
	No	No
3.0-3.4	5	1
3.5-3.9	9	8
4.0-4.4	15	24
4.5-4.9	19	23
5.0-5.4	14	20
5.5-5.9	10	13
6.0-6.4	6	4
6.5-6.9	6	2
7.0-7.4	5	0
7.5-7.9	3	0
Range	Level mg % 3.0-7.8	Level mg % 3.1-6.9
Mean \pm S.E.	5.13 \pm 1.1	4.85 \pm 0.7

*Normal range of serum uric acid is 2.0-5.0 mg. per cent.

†Several values were not obtained owing to sampling errors or laboratory wastage etc.

in the coronary group will be discussed in the sections that follow

Both the coronary heart disease group and the matched control group were subdivided by age, and the average serum uric acid levels were calculated. It was obvious that there was no change of serum uric acid with age. This contrasts with the change in serum total cholesterol which showed a small but significant rise with age in both groups.

The CUP Index

It is evident from the discussion in Chapter VIII that there are factors other than the level of serum cholesterol responsible for the deposition of cholesterol in the intima. The colloidal stability, the quantity and quality of the surface active agents, and the intimal permeability may play a role in the extent to which cholesterol is deposited in the intima. It has been shown (Chapter VIII) that the ratio of serum total cholesterol to lipid phosphorus is probably more important than the level of either component. Lecithin (80 per cent of serum phospholipids) may act like a cationic surface active agent. Uric acid in its lactam state contains three free hydroxyl ions and theoretically could act as an anionic surface active agent.

Because of the possibility that the phospholipids and uric acid may oppose each other as surface active agents, and because of the theoretical possibility that actual removal of cholesterol to the intima may be brought about by the force of the entire combination of surface active agents (of which lecithin and uric acid are only two), it was decided to combine the uric acid value with the total cholesterol/lipid phosphorus ratio. Thus if K represents the CUP index or numerical value of this total relation

$$K = \text{serum uric acid mg per cent} \times \frac{\text{serum total cholesterol mg per cent}}{\text{serum lipid phosphorus mg per cent}}$$

The additional abnormal factor of serum uric acid may prove to have some enhancing effect on the deposition of serum cholesterol in the intimal tissue by alteration of the permeability, as do some of the surface active agents.

In Figure 2 and Table 2 are given the CUP indices for the matched control group and coronary heart disease group. It will be shown that a consideration of all three variables known to be

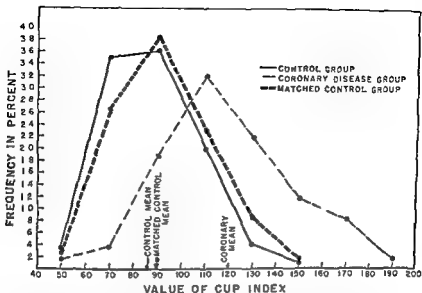


FIGURE IX-2 Frequency distribution of CUP index in coronary heart disease group of 59, unmatched control group of 146, and matched control group of 83. The polygons of the two control groups are practically identical while the polygon of the coronary group shows signs of distinct separation at the higher levels.

TABLE IX-2 CUP index* in coronary heart disease group of 59† males and matched control group of 83‡ males

Index level	Coronary group	Control group
	No.	No.
40-59	1	2
60-79	3	2
80-99	11	32
100-119	19	19
120-139	13	7
140-159	7	1
160-179	5	0
180-199	1	0
Range	Index level 49-188	Index level 58-151
Mean \pm S.E.	119 \pm 4	90 \pm 2
	% below 119 50.0%	% below 119 90.4%

Serum total cholesterol mg. \times serum uric acid mg. \times

serum l.p.d. phosphorus mg.

†For 38 patients either uric acid or l.p.d. phosphorus was not determined.

‡For 14 controls either uric acid or l.p.d. phosphorus was not determined.

§At least 50 per cent are always below the mean.

associated with coronary heart disease is more meaningful than any one variable considered individually

The mean CUP index of the coronary heart disease group was significantly higher than that of the matched control group. It is interesting that 90.4 per cent of the matched control group were below the mean value of the coronary heart disease group. Of the 83 matched controls only 1 exceeded 147 which represents the value of one standard deviation above 119 (the mean of the coronary heart disease group).

The CUP index was also determined for the larger group of unmatched controls. The distribution of the index was essentially similar to that of the matched control group, the mean was 87 (see Figure 2).

Uric Acid and Morphological Characteristics

Since it had been shown that the highest levels of serum total cholesterol occur in the mesomorphs who experience coronary heart disease, it was decided to study the relations between serum uric acid and morphological characteristics in both the matched control and coronary groups. Consequently coefficients of correlation were determined between serum uric acid and height, weight and ponderal index.

Certain information may be gathered from the coefficients of correlation (Table 3). (a) there were insignificant correlations between uric acid and height in the coronary heart disease group and the matched control group. (b) although the positive correlations between weight and uric acid were fairly small, they did attain statistical significance for both groups. (c) there were small but significant negative correlations between ponderal index and uric acid in both groups.

TABLE IX-3 Uric acid coefficients of correlation in coronary heart disease group and matched control group, each of 92 males*

Correlation with serum uric acid	Coronary group	Control group
Height	+ .10 \pm .10	+ .05 \pm .10
Weight	+ .23 \pm .10	+ .26 \pm .10†
Ponderal index	- .22 \pm .10	- .25 \pm .10†

Owing to sampling errors, laboratory wastage, etc. 5 samples were not obtained.

†Difference is significant.

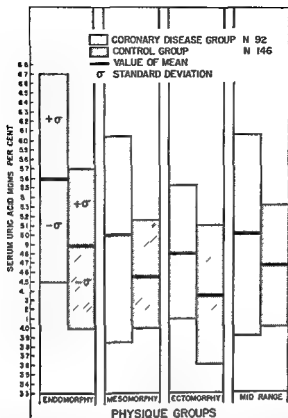


FIGURE IX-3 Serum uric acid levels by physiques in coronary heart disease group and unmatched control group. A comparison of the physiques within the coronary and unmatched control groups shows that in both the endomorphs had a higher level of serum uric acid than ectomorphs. A comparison of the coronary group with the unmatched control group shows higher levels in the coronary group for all physiques, the largest difference occurring in the category of endomorphy.

Thus linear measurement per se is unrelated to serum uric acid but as the weight and body mass of the individual increase as reflected by the ponderal index the serum uric acid has a tendency to be elevated. Such rough estimates of physique suggested that dominant ectomorphs would have lower levels of uric acid in the serum while dominant mesomorphs and endomorphs would have higher levels of serum uric acid. To evaluate these suggestions more critically correlations were made (see Figure 3) between the Sheldonian classifications (endomorphs, mesomorphs and ecto-

TABLE IX-4 Serum uric acid by physiques in coronary heart disease group of 92 males* and unmatched control group of 146 males

Physique	No of cases	SERUM URIC ACID MG %	
		Range	Mean \pm S.E.
ENDOMORPHS			
Coronary	23	3.6-7.6	5.61 \pm .23
Control	51	3.1-6.9	4.87 \pm .12
difference			†
MESOMORPHS			
Coronary	41	3.2-7.7	4.98 \pm .18
Control	34	3.6-5.4	4.59 \pm .09
difference			n.s.
ECTOMORPHS			
Coronary	9	3.9-6.1	4.80 \pm .23
Control	34	2.9-5.8	4.34 \pm .12
difference			n.s.
MID RANGE			
Coronary	19	3.2-7.1	5.01 \pm .27
Control	27	3.8-6.2	4.65 \pm .12
difference			n.s.

*In 5 cases serum uric acid was not determined owing to sampling errors and laboratory wastage etc.

†Highly significant.

N.s.—Not significant.

morphy) and serum uric acid. It was thought that these correlations would be more meaningful than the correlations between height, weight and ponderal index, because the actual make up of the body mass could be defined more accurately (see Table 4 and Figure 3).

Several striking features in the distribution of serum uric acid among the physiques of both the coronary heart disease group and the unmatched control group are these: (a) endomorphs possessed the highest level of serum uric acid; (b) ectomorphs possessed the lowest level of serum uric acid; (c) this contrast was statistically significant. The only other contrast between body types which was significant was within the coronary heart disease group where the endomorphs differed statistically from both the mesomorphs and the ectomorphs.

The only comparison between the coronary heart disease group and the control group which was significant was that for the endomorphs. From such observations it is reasonable to suggest that hyperuricemia, endomorphy and coronary heart disease are interrelated in some as yet unexplained manner.

Conclusions

The presence of an elevated serum uric acid in coronary heart disease in the absence of renal damage or any other conventional cause such as excessive protein catabolism poses an interesting question. Is the excessive uric acid in the serum due to a positive uric acid balance with an excessive endogenous production as the dominant factor? Is this mechanism a genetic phenomenon? There is evidence that hyperuricemia is due to an autosomal dominant gene but only a portion of the heterozygotes develop gout (Smyth et al 1948)

The uric acid-endomorphic relation permits further insight into the relative importance of endomorphy or fatty tissue in coronary heart disease. It has been shown that the coronary physique is mesomorphic (muscular) with endomorphy (softness roundness) as a secondary characteristic. It was also shown that the level of total cholesterol in the serum is on the average higher in coronary heart disease and that this higher level appears greatest in the mesomorphic group. The uric acid studies in the coronary heart disease group revealed that serum uric acid is highest in the dominant endomorphs. Thus it may be possible to relate the mesomorphic component in coronary heart disease to the maximal levels of serum cholesterol and the endomorphic component to maximal levels of serum uric acid.

The significant difference of the mean levels of serum uric acid between those of the same body build in the matched control group and the coronary heart disease group indicates that additional factors other than body build are contributing to this difference the cause of which is unknown at present.

What harmful effects on the intima may be attributed to hyperuricemia? Does uric acid act as an intimal conditioning agent (surface active agent) which is conducive to cholesterol deposition especially if there is an instability in the colloidal state of the serum lipids? These problems have not been adequately studied and can not be discussed at this time.

The CUP index may or may not prove to be especially useful in pre selecting those who are prone to coronary heart disease. It does separate the normal group from the coronary heart disease group more effectively than any other index we have at the present time.

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CHAPTER X

Diet Cholesterol Ingestion and Atherosclerosis

DIETARY factors have been implicated in the pathogenesis of atherosclerosis. A general relation of the disease to nutrition has been claimed on the grounds that atherosclerosis is more frequent in individuals who are overweight (Wilens 1947) and that it is decreased in the population during periods of famine (Aschoff 1924 Keys 1953). Whether there is a causal relation between atherosclerosis and nutrition however is open to considerable question. The relation of weight to coronary heart disease has already been discussed in Chapter IV where it was shown that in the present study the patients were actually not overweight as compared with the controls. And as far as malnutrition is concerned (see below under Studies by Other Investigators) the presence of many variables makes it uncertain whether this condition leads to death from atherosclerosis. There is e.g. the fact that susceptibility to other diseases is lowered by poor nutrition with the result that fewer undernourished people live to the age at which degenerative disease sets in.

A major topic of investigation in this study was the relation of cholesterol ingestion to atherosclerosis. Claims have been made that atherosclerosis is less frequent in countries where cholesterol is ingested in small quantities than in those where amounts of cholesterol ingested are greater (Dock 1946 Snapper 1947). These specific questions will be discussed later in the chapter.

Source of Cholesterol in Atherosclerosis

It is well known that serum total cholesterol is frequently elevated in coronary heart disease. It is also well known that atherosclerotic plaques which are responsible for coronary heart disease contain cholesterol and cholesterol esters to a greater degree than does the surrounding arterial tissue. These two known facts are

thought by many observers to be causally related. They reason that (a) where cholesterol is ingested in large quantities it produces an elevated serum cholesterol, and (b) an elevated serum cholesterol will eventually produce atherosclerosis. Chapter VIII has reviewed two aspects of evidence that opposes these contentions: (a) the serum cholesterol distribution curves of both the control group and the coronary heart disease group overlap to a considerable degree, and (b) the interrelations of the other lipids such as phospholipids are as important in the deposition of cholesterol as cholesterol itself. Furthermore, no one has demonstrated satisfactorily in human beings the source of the cholesterol in the atherosclerotic plaques. Does it come from the cholesterol that exists in the serum? If so, is the source mainly exogenous or endogenous? Does cholesterol arise from the degenerating intimal cells? Is it synthesized by the intimal tissue in sufficient quantities to produce atheromatous plaques? Is it brought to the plaques by the Kupffer cells or by some other means? These questions were considered in the course of the present project.

Relation of ingested cholesterol to serum cholesterol

DIET RECORD In order to obtain data on which to base our consideration of these questions, a diet history was compiled for 90 males with coronary heart disease and for an unmatched control group of 139 healthy males* covering the period at least 10 years prior to their myocardial infarction. Information designed to reveal intake of cholesterol and uric acid stressed not only the foods that obviously contain cholesterol and uric acid but also those that contain the greatest percentage of amino acids which are thought to be cholesterol precursors (Duncan 1947). Accordingly, the diet record was adequate so far as protein and fat intake is concerned.

The total daily fat and protein intake calculated from the diet cards (see Appendix D) is recorded in Table 1. The difference between the means of the two groups is significant. The information, however, does not indicate the total caloric intake of either group which should also include calories supplied in the form of carbo-

*All data in this chapter are based on these numbers of patients and unmatched controls. In each group, records were lacking for 7 men.

TABLE V-1 Fat and proteins ingested by coronary heart disease group of 90 males and unmatched control group of 139 males

	CORONARY GROUP		CONTROL GROUP	
	<i>Mean daily intake gm</i>	<i>Calories</i>	<i>Mean daily intake gm</i>	<i>Calories</i>
Fats	66	594	90*	810
Proteins	52	208	62*	248

*Difference is significant.

hydrates consequently it is not known whether the coronary heart disease group had a greater or lesser caloric intake than the control group. Although the diet record thus affords an inadequate assessment of carbohydrate intake it may be reasonably assumed that the total amounts of carbohydrates were proportionate to those of fats and proteins and hence like them were not excessive in either group.

FINDINGS BASED ON DIET RECORD Because of the claims that increased ingestion of cholesterol will produce an elevated level of serum cholesterol it was decided (a) to determine the average amount of cholesterol ingested per week for both the coronary heart disease group prior to infarction and the control group and (b) to correlate the amount of cholesterol ingested with the level of cholesterol in the serum for these two groups. The results are summarized in Tables 2 and 3.

The control group on the average ingested significantly more cholesterol than the coronary heart disease group (18 per cent more) but had significantly less cholesterol in the serum than the coronary group (224.4 mg per cent as against 286.5 mg per cent see Chapter VIII Table 7).

TABLE V-2 Mean cholesterol intake in coronary heart disease group of 90 males and unmatched control group of 139 males

	<i>No of cases</i>	GM PER WEEK	
		<i>Range</i>	<i>Mean \pm S.E.</i>
Coronary group	90	6-66	3.3 \pm .15
Control group	139	6-94	3.9 \pm .1

S significantly greater

TABLE X-3 Ingested amounts and serum levels of cholesterol for 10 individuals with highest and 10 with lowest cholesterol ingestion in coronary heart disease group and unmatched control group

	Coronary patients mean \pm S.E.	Controls mean \pm S.E.
10 WITH HIGHEST CHOLESTEROL INGESTION		
ingested amount (gm per week)	5.67 \pm .15	6.98 \pm .31
serum total cholesterol (mg %)	288 \pm 21.9	213 \pm 11.4
10 WITH LOWEST CHOLESTEROL INGESTION		
ingested amount (gm per week)	1.34 \pm .10	1.37 \pm .13
serum total cholesterol (mg %)	271 \pm 14.2	222 \pm 15.6

As a further check on the degree of correlation between cholesterol ingestion and serum cholesterol it was decided to determine the level of serum cholesterol in those who ingested the most and the least cholesterol in both coronary and control groups. The results are summarized in Table 3.

It is clear that in the coronary heart disease group in spite of the lower average *ingestion* of cholesterol, both the individuals who ingested large quantities and those who took small quantities have an average *serum* total cholesterol significantly higher than that of the control group. Furthermore the level of serum total cholesterol within the coronary group does not change appreciably with these large differences in cholesterol ingestion.

From these results it is apparent that a factor or factors in addition to ingested cholesterol is important. This conclusion gains further support from the small and not significant coefficients of correlation between the amount of ingested cholesterol and the level of serum cholesterol for both groups: +.05 for the unmatched control group and -.09 for the coronary heart disease group. The lack of correlation is well shown in Figure 1. There is thus practically no correlation between the amount of cholesterol ingested and the level of cholesterol in the serum.

This fact, in combination with the finding that serum cholesterol was higher in the coronary than in the control group suggests that a major source of cholesterol could possibly be endogenous. This viewpoint is currently espoused by Gould (1951) and Bloch (1954). Bloch's work with labeled acetate and squalene has given much information on steroid biogenesis.

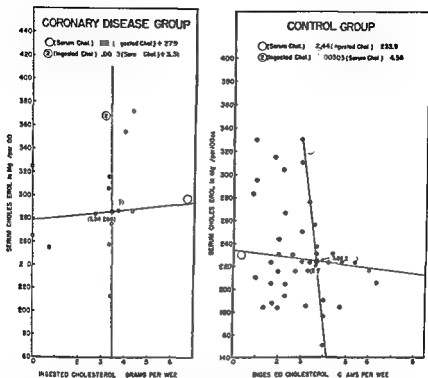


FIGURE X-1 Scattergrams with regression lines showing relation of ingested total cholesterol to serum total cholesterol in coronary heart disease group of 90 males and unmatched control group of 139 males. The coefficients of correlation were not significant being -0.09 ± 0.08 and $+0.05 \pm 0.11$ for the coronary group and the control group respectively.

FINDINGS BASED ON TEST MEALS The relation of ingested cholesterol to serum cholesterol was studied not only by means of the diet record, but by test meals. No attempt was made to solve all the numerous problems that may arise from variations of diet, but the tests were designed to determine the effects on the levels of serum total cholesterol and cholesterol esters of coronary patients that will be produced by

Test 1 *Fat* ingestion of 25 gm of butter and 3 slices of white toast with a cup of plain tea

Test 2 *Fat and cholesterol* ingestion of 25 gm of butter and 5 gm of cholesterol in the form of egg yolk

Test 3 *Cholesterol* ingestion of 5 gm of cholesterol in the form of egg yolk mixed as an eggnog

Test 4 *Low cholesterol diet* over a period of 6 to 30 months

In all tests determinations were made of changes in serum total cholesterol, cholesterol esters, and cholesterol esters/total cholesterol ratio

The first three tests were performed on coronary patient No 049. On successive days his total cholesterol and cholesterol esters were determined after an all night fast; then he was given a test meal on the first day at 11 A.M. on the second and third at 9 A.M. The results given in Tables 4, 5, and 6 show that in Tests 1 and 3 the levels and ratios of serum total cholesterol and cholesterol esters were practically unaffected by the test procedures, whereas in Test 2 they were increased to a slight degree.

The conclusions derived from these three experiments are consonant with the observation that ingested cholesterol in physiological amounts will best be absorbed when absorbable fats (usually unsaturated fatty acids) are present in quantitative relations. Similar observations have been made by Steiner and Domanski (1941) and Cook (1936, 1937).

Test 4, conducted on coronary patient No 052, indicated that when the ingested cholesterol is restricted to approximately 150 mg daily there is a rapid decline in the level of serum total cholesterol and serum cholesterol esters which reach their minimal level in about 10 to 18 days (see Figure 2). This minimal level is usually from 25 to 40 per cent lower than the original cholesterol level and 30 to 50 per cent lower than its original esterified component. However, the levels do not remain stationary in spite of a continued low

TABLE X-4 Serum cholesterol levels after Test 1

	<i>Fast ng before 11 00 A M meal</i>	<i>1 7 45 P M</i>	<i>2 45 P M</i>	<i>4 45 P M</i>	<i>6 45 P M</i>
Total cholesterol (mg %)	630	585	537	489	489
Cholesterol esters (mg %)	354	345	270	—	—
Cholesterol esters	56	58	50	—	—
Total cholesterol					

TABLE X-5 Serum cholesterol levels after Test 2

	<i>Fasting before 9 00 A M meal</i>	<i>10 0 A M.</i>	<i>1 20 P M</i>	<i>2 0 P M</i>	<i>4 30 P M</i>
Total cholesterol (mg %)	693	708	729	663	651
Cholesterol esters (mg %)	347	342	367	375	412
Cholesterol esters	50	48	50	56	63
Total cholesterol					

TABLE X-6 Serum cholesterol levels after Test 3

	<i>Fa s t b f o e 9 00 A M meal</i>	<i>11 45 A M</i>	<i>2 10 P M</i>	<i>5 10 P M</i>
Total cholesterol (mg %)	577	537	537	531
Cholesterol esters (mg %)	399	336	347	366
Cholesterol esters	69	63	65	68
Total cholesterol				

RESTRICTED CHOLESTEROL INTAKE AND SERUM CHOLESTEROL

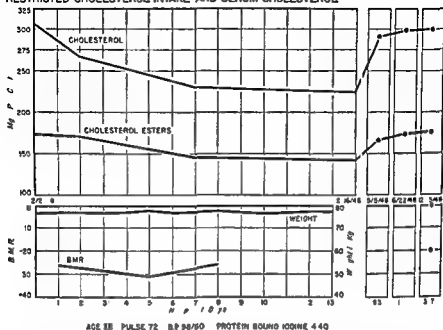


FIGURE X-2 Record of patient hospitalized for a period of 2 weeks and then followed very closely for 10 months at home. While in the hospital the patient was placed on a low cholesterol diet which was continued for 10 months. The serum total cholesterol fell from 310 mg per cent to 235 mg per cent in 7 days and remained at that level for approximately a month. Thereafter the cholesterol rose steadily, reached its former level within 4 1/2 months and remained at that level.

cholesterol diet and when the patient is studied for longer periods a slow rise in total cholesterol and cholesterol esters is observed. The levels attain their original values in 7 to 12 months and then remain high.

Thus it may be concluded that the effect of a low cholesterol diet is to produce an immediate lowering of serum total cholesterol and esterified cholesterol. But this trend ceases within a fortnight and even if the diet is continued the tendency reverses itself and the levels of total cholesterol and esterified cholesterol rise slowly and reach their original values within a year.

One might presume that the original lowering of cholesterol is due to restriction of the exogenous source. However, since serum cholesterol is derived from both exogenous and endogenous sources it is probable that when the former source is removed the latter

becomes more active and eventually restores the equilibrium. It is noteworthy that there was no significant fluctuation in weight during the course of these experiments.

Similar observations were made on 6 other coronary heart disease patients and in each case the pattern was the same (See Figure 3 for a summary of these 6 cases.) On the basis of this evidence one may seriously question the merits of a low cholesterol diet and its role in lowering the serum cholesterol. However, since the relation between an elevated serum cholesterol and atherosclerosis is not entirely clear, one must reserve judgment on the capacity of the low cholesterol diet to prevent the disease. The ingestion of lipids may play a role in cholesterol deposition, as suggested by Moreton (1948). Walker (1953) summarized the effects of dietary restriction on serum lipids and has demonstrated that weight reduction reduces serum lipids.

INGESTION OF CHOLESTEROL PRECURSORS Schoenheimer and his school have demonstrated by the use of deuterium labeled precursors that cholesterol may be synthesized in the mouse (Schoenheimer and Breusch, 1933). Furthermore, it has been shown that

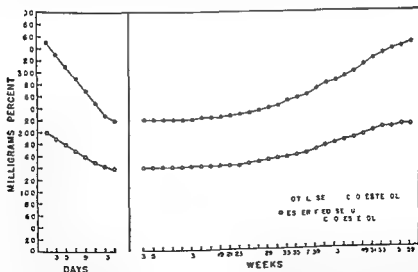


FIGURE X-3 Effect of prolonged restriction of dietary cholesterol: summary of data on 6 patients. After a transient drop the level of serum total cholesterol gradually increased (presumably by endogenous means) to its former point and remained there while the patients were on the low cholesterol diet.

cholesterol is synthesized from amino acids such as leucine and alanine from acetic acid, and from fatty acids such as myristic and butyric acids (Duncan, 1947, Rittenberg and Bloch 1945 Ponticorvo et al 1949) In all probability similar mechanisms of synthesis exist in man, despite the failure to demonstrate all of them as yet In our study analysis of the diet records revealed no correlation between the amounts of these substances in the diet and the level of serum cholesterol

Relation of serum cholesterol to atherosclerosis

The phospholipids in a manner as yet unknown, may act as a colloidal stabilizer by maintaining the serum cholesterol in suspension and preventing its tendency to be attracted to the intimal tissue and thus to be deposited there (see Chapter VIII Ladd et al) Moreton (1948) brought out an interesting theory supported by experimental evidence, of the etiology of atherosclerosis He demonstrated that fat particles (chylomicrons) appearing in normal plasma during alimentary hyperlipemia are of colloidal size and upon ultracentrifugation, are shown to consist of mainly neutral fats and lipid phosphorus in addition to minute quantities of cholesterol and other substances (Gofman 1950) Moreton suggests that the cumulative effect of fatty meals over a lifetime by producing transient showers of large lipid particles in the plasma is the underlying cause of atherosclerosis in normal human beings Following this observation Becker and his associates (1949) showed that hyperchylomicronemia occurs at any age following fat containing meals However the intensity, size, and duration of the chylomicron state increases with the age of the individual The abnormal postabsorptive chylomicron state in older human beings is restored to the normal state by the use of detergents and lipases

These three separate observations by Ladd and his co workers (see Chapter VIII) by Moreton and by Becker and his associates are interrelated and suggest that a disturbance in the colloidal state of the blood may be one of the most important factors in atherosclerosis These aforementioned studies support our observation that cholesterol is not the only factor involved in atherosclerosis (Gertler and Garn 1950) In addition they demonstrate the necessity of increasing the rapidity of lipid absorption and utilization in older individuals The Moreton hypothesis still does not clarify the ques

tion of cholesterol ingestion and its relation to atherosclerosis. It does not explain the mechanism of atherosclerogenesis particularly when there is practically no cholesterol available in the hyperchylomicronemic state.

Gofman and his co workers (1950) have shown that the blood of individuals with atherosclerosis contains an increased concentration of large cholesterol molecules of the class S_r 10-20. By the use of a low fat low cholesterol diet the concentration of this large molecule S_r 10-20 was decreased to normal values. On this basis Gofman recommends the use of a low cholesterol low fat diet. Further study of this moot point is in progress by various groups of investigators (see Walker 1953).

General Relation of Cholesterol Ingestion to Atherosclerosis

Diet in other countries

A possible association between a low incidence of atherosclerosis and a low ingestion of cholesterol has been suggested by various reports stating that atherosclerosis in the Chinese and Okinawans is uncommon presumably because of a diet which is normally low in cholesterol. However there is no conclusive evidence that the incidence of either atherosclerosis or coronary heart disease is lower in China than elsewhere. Hospital records in China are not so well kept as they are in the United States and local territorial and national death records are not so accurate there as in this country. Even if they were extensive corrections of the statistical data would be required before the interpretations could be considered valid. For example there is a smaller percentage of the Chinese than of the American population falling into the age groups in which atherosclerosis is common because of the high rate of infant mortality and the high death rates from other causes such as tuberculosis and other infectious diseases in China (Snapper 1947). Consequently a confirmed lower death rate from atherosclerosis in China might reflect merely the fact that the age distribution is lower.

Similarly the purported low incidence of coronary heart disease or atherosclerosis in Okinawans has been considered to be causally related to the diet which is said to contain little or no cholesterol. In reviewing P. E. Steiner's material on autopsies performed on 150 Okinawans (51 males and 99 females) from 1 to 100 years of age it is evident that 7 individuals (6 males over 55 years and 1 female

of 91) had visible aortic atherosclerosis (P E Steiner 1946) Thus 6 males out of 51 who were examined (12 per cent) showed atherosclerosis In another series of autopsies performed on about 200 Okinawans during World War II the incidence of atherosclerosis in both men and women almost approximated that observed in the United States (Zimmerman 1954)

Studies by other investigators

Further support of the dietary causation of atherosclerosis is offered by those who quote as evidence (a) the decrease in atherosclerosis in Germany immediately following World War I (Aschoff 1924) (b) the lower incidence of atherosclerosis in chronic alcoholics (Wilens 1947) and (c) the decrease of atherosclerosis in ill nourished and lean individuals (Wilens 1947) The common denominator in all three categories appears to be a low fat intake due to dietary restriction Critical examination of the data reveals that the authors' claims are based upon the assumption that in these groups the fat and hence the cholesterol intake is decreased thereby decreasing the propensity of the individual to develop atherosclerosis There is no further evidence however to support these assumptions Actually ill nourished individuals and chronic alcoholics are more prone to other diseases at an early age and hence do not always attain the age at which degenerative diseases manifest themselves However much more complete world wide study is needed

Other evidence for a relation between cholesterol ingestion and atherosclerosis is based on experiment There are data to indicate that excessive cholesterol feedings may produce atherosclerosis in the rabbit (Anitschkow and Chalator 1913) or dog (Steiner and Kendall 1946) Such evidence has been accepted as applicable to man by some observers (Leary 1949) Others are reluctant to make this acceptance because (a) the amount of cholesterol employed in these experiments far exceeds the highest physiological level of ingestion by man and (b) the lesions are distributed mainly in the distal arteries and to a lesser degree involve the coronary arteries Duff (1935) has questioned whether the disease process in man and in rabbits is comparable

Summary

It has been claimed from evidence based on (a) animal experiments (b) statistical studies in various sections of the world

and (c) human studies that dietary intake particularly low cholesterol diet, influences atherosclerogenesis. However in a critical analysis of the data it is observed that the statistics on the reportedly low incidence of atherosclerosis in countries such as China are probably distorted greatly. The animal feeding experiments reveal an increased incidence of atherosclerosis in those animals which are fed cholesterol in large quantities. These experiments however may or may not be applicable to man. In man it has been shown that the amount of cholesterol ingested has little bearing on the level of serum cholesterol. Although it has been demonstrated that an association exists between the level of serum lipids and clinical atherosclerosis there are no studies available which demonstrate a causal relation between ingested lipids including cholesterol and atherosclerosis either from a clinical viewpoint or a pathologic viewpoint. There may however be other dietary factors such as ingestion of fat or of cholesterol precursors which do relate to atherosclerosis. The whole question of dietary relation to atherosclerosis still remains an area for investigation for there is good supportive evidence on both sides.

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CHAPTER XI

The Oxidation Reduction Potentials of Saliva

It is known that a solution containing oxidizable or reducible substances shows a characteristic electrical potential. In all solutions the electromotive force (EMF) is dependent upon the concentration of the solute, the pH, and the temperature. But in body fluids oxidation reduction potentials (E_{c^*}) are dependent not only on physical variables but also on the relations of enzymes, coenzymes and substrates and their interaction with electrolytes (inorganic and/or organic salts). The potentiometer readings in millivolts of solutions of the latter type show a change with time which is referred to as drift in poise. This is the result of the change in oxidation reduction potentials and may be altered easily by the addition of oxidants or reductants. For further details concerning the mechanisms of enzymatic oxidations and reductions in cellular metabolism, the reader may consult LuValle's and Goddard's excellent review paper (1948) and books by Michaelis (1925, 1930), Hewitt (1936), and Lardy (1949).

Michaelis (1925) has reported on the initial oxidation reduction potential in whole blood. Eisenbrandt (1943) studied the salivary potentials of five adults and found that the initial oxidation reduction values of his subjects did not vary significantly from each other in daily observations. Eisenbrandt dealt primarily with the initial EMF values but did not emphasize them in relation to time.

In a study to determine the degree of association between dental caries and the values of oxidation reduction potentials of fresh saliva (obtained without the use of physical or chemical stimulants) as a function of time, it was found that among the children examined at Forsyth Dental Infirmary in Boston several dropped rapidly in their salivary potentials toward negative values. These children appeared to fall into a distinct group and it was believed that further

E_c readings are the EMF readings taken directly from the Beckman potentiometer with the calomel platinum electrode combination, expressed in millivolts.

investigation was merited. Since the case histories were readily available, they were studied carefully. It was found that among these children were some whose parents were particularly prone to degenerative cardiovascular disease. This fact was made known to the members of the present project who then made further studies.

Procedure

The studies dealt with 66 individuals who had had myocardial infarction and a group of 73 healthy working males roughly similar in age, ethnic origin, body build, and mouth condition, drawn from the matched control group. Those taking the test had not eaten, drunk, or smoked during the previous two hours. Approximately 1.5 ml of saliva were collected from each person directly into a 5 ml beaker. This freshly collected sample was placed immediately in a Beckman potentiometer (laboratory model G) with the standard Beckman calomel platinum electrodes inserted in position 1/16 inch apart in the saliva. The door to the room was closed to ensure uniform atmosphere. Readings were made directly from the designated scale on the instrument. The salivary sample was kept inside the chamber with the electrodes fixed in the solution. Readings were made first after 15 seconds and then at 1 minute intervals up to 5 minutes and following that at 5 minute intervals up to 30 minutes.

In order to ensure experiments that would be reliable over a reasonable period of time and that could be duplicated, repeated tests were performed on 6 'normal' persons and on 3 patients who had had myocardial infarction.

Duplicability of Patterns of Oxidation Reduction Potentials

Various patterns were found in the saliva. The patterns differed in the numerical level of the oxidation reduction potentials and in the rate of change of the level with time. Of the various possible combinations of starting potential and rate of change, the four in Figure 1 represent both the extreme and the modal patterns.

The question arises immediately as to whether such differences as those shown in Figure 1 are stable. Are the patterns characteristic of an individual? Can they be duplicated in that individual? In order to determine the reliability of the salivary oxidation reduction potential pattern, several persons, both normal and with coronary heart disease, were tested over various periods of time.

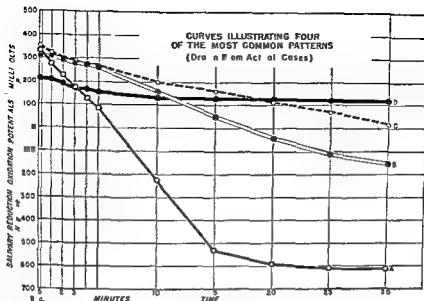


FIGURE VI-1 The four most common patterns of oxidation reduction potentials of saliva observed over a period of 30 minutes. The majority of cases started at +300 millivolts but the final readings on the Beckman potentiometer varied from +100 millivolts to -600 millivolts.

- A High positive at 15 seconds (> 300) to low negative at 30 minutes (-600) rapid change
- B High positive at 15 seconds (> 300) to moderate negative (-150) at 30 minutes moderate change
- C High positive at 15 seconds (> 300) to approximately 0 at 30 minutes slower change
- D Moderate positive at 15 seconds (> 200) changing slowly but still positive after 30 minutes slow change

Coronary subject

A male married who had experienced a myocardial infarction at the age of 40 was examined on February 11 1949 and subsequently on May 24 1949 three weeks after an operation for a detached retina. The test of the oxidation reduction potential of his saliva was repeated under oil on October 5 1949. This case illustrated the duplicability of results in the coronary population in that both the rate of change and the total drop were repeatable. The individual minute readings matched less well. Reliability and the possibility of duplication are necessary criteria for the application of the oxidation reduction potential testing procedure to saliva in a medium that has been little surveyed by this technique. The relia

TABLE XI-1 Potentiometer readings in millivolts of coronary subject (Year 1949)

Time	2/11	5/24	10/5
15 sec	+ 240	+ 245	—
1 min	+ 140	+ 222	—
2 min	+ 70	+ 192	+ 162
3 min	0	+ 172	+ 140
4 min	— 40	+ 156	+ 130
5 min	— 60	+ 138	+ 112
10 min	— 205	+ 20	— 100
15 min	— 570	— 114	— 315
20 min	— 576	— 261	— 438
25 min	— 576	— 377	— 451
30 min	— 578	— 451	— 471

bility of the technique under conditions similar to those outlined in this report is as good as may be expected in biological work. This degree of reliability is well illustrated in Table 1.

Control subject

A healthy male aged 24 was tested twice on 2 successive days given a respite for 5 days and then retested three times on 3 successive days following these five repeated tests the subject was further tested at weekly intervals for 3 weeks and finally after a month's freedom from testing was retested. All tests were administered at 10 00 A M. In Table 2 the mean value and the actual values for each test time are listed. Note that the potentiometer values are relatively constant during this period of 58 days (March 15 to May 12).

TABLE XI-2 Potentiometer readings in millivolts of control subject (Year 1949)

Time	3/15	3/16	3/21	3/22	3/23	3/31	4/6	4/13	5/17	Mean
15 sec	+ 280	+ 282	+ 294	+ 300	+ 298	+ 296	+ 286	+ 290	+ 290	+ 290
1 min	+ 272	+ 274	+ 278	+ 290	+ 286	+ 274	+ 278	+ 282	+ 284	+ 279
2 min	+ 262	+ 262	+ 274	+ 280	+ 281	+ 256	+ 266	+ 277	+ 276	+ 270
3 min	+ 254	+ 256	+ 272	+ 271	+ 273	+ 246	+ 249	+ 272	+ 269	+ 262
4 min	+ 250	+ 249	+ 264	+ 261	+ 266	+ 239	+ 251	+ 262	+ 261	+ 255
5 min	+ 244	+ 242	+ 261	+ 252	+ 266	+ 231	+ 248	+ 254	+ 254	+ 250
10 min	+ 228	+ 228	+ 242	+ 238	+ 231	+ 212	+ 222	+ 232	+ 230	+ 229
15 min	+ 212	+ 212	+ 232	+ 224	+ 227	+ 200	+ 208	+ 210	+ 194	+ 211
20 min	+ 201	+ 206	+ 225	+ 211	+ 218	+ 192	+ 198	+ 189	+ 180	+ 202
25 min	+ 192	+ 152	+ 221	+ 197	+ 211	—	+ 190	—	+ 172	+ 190
30 min	+ 178	+ 148	+ 212	+ 182	+ 203	+ 169	+ 182	+ 136	+ 164	+ 174

TABLE XI-3 Potentiometer readings in millivolts of coronary heart disease group of 66 males*

Time	No. in group	Range	Mean \pm S.E.
15 sec	66	+340 to +100	+270.5 \pm 5.93
1 min	59†	+330 to -80	+239.0 \pm 8.18
2 min	60	+292 to -138	+213.0 \pm 9.67
3 min	57	+284 to -170	+179.5 \pm 12.40
4 min	61	+278 to -204	+157.0 \pm 13.90
5 min	63	+272 to -233	+133.5 \pm 16.74
10 min	60	+250 to -550	+0.5 \pm 28.77
15 min.	62	+232 to -632	-98.5 \pm 33.76
20 min	61	+225 to -642	-156.5 \pm 36.80
25 min	61	+220 to -642	-180.5 \pm 35.89
30 min	62	+210 to -648	-246.5 \pm 36.70

*Tests were not attempted on 31 males

†Occasionally readings were not obtained.

Oxidation Reduction Potentials in the Coronary and Control Groups

Oxidation reduction potentials were determined at intervals of from 15 seconds to 30 minutes in saliva from 66 males who had had myocardial infarction before the age of 40 and whose ages ranged from 25 to 52 at the time of examination and a control group of 73 healthy working males (mean age in both groups is 39). The mean results for each time interval are given for both groups in Tables 3 and 4.

A statistical analysis of the data revealed a significant difference starting with the 2 minute value and extending through the 30 minute value.

TABLE XI-4 Potentiometer readings in millivolts of control group of 73 healthy males

Time	No. in group	Range	Mean \pm S.E.
15 sec	73	+352 to +200	+280.0 \pm 5.14
1 min	70*	+332 to +150	+253.0 \pm 5.41
2 min	69	+312 to +100	+243.0 \pm 6.19
3 min	67	+300 to 0	+204.0 \pm 6.76
4 min	63	+289 to -50	+195.0 \pm 8.11
5 min	73	+284 to -100	+171.5 \pm 9.23
10 min	73	+262 to -358	+93.5 \pm 16.49
15 min.	71	+252 to -467	+23.5 \pm 27.71
20 min	71	+246 to -516	-35.5 \pm 28.09
25 min	69	+240 to -530	-85.5 \pm 29.39
30 min	70	+240 to -554	-134.5 \pm 30.23

*Occasionally readings were not obtained.

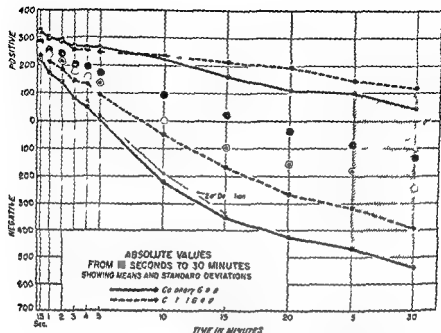


FIGURE XI-2 Oxidation reduction potentials of saliva in coronary heart disease group of 66 males and control group of 73 males. The ordinate represents millivolts; the abscissa, time in minutes. The black dots and the circled dots represent the means at the various time intervals for the control group and the coronary group respectively.

The data for both series have been put into graph form in Figure 2. Included are the mean values for each group at various time intervals and the ± 1 standard deviation limits for both groups. Approximately 68.26 per cent of either group is included between these two limits.

From the data plotted in Figure 2 several characteristics are at once apparent. The general trend over a period of time for both groups was downward from a mean starting oxidation-reduction potential of approximately +280 millivolts to potentials of -152 and -246 millivolts respectively at 30 minutes. The coronary heart disease group was distinguished by being below the control group at all intervals; hence the difference was systematic. Furthermore, the absolute difference between the two groups tended to be larger with elapsed time.

In spite of the significant differences in the means, there was a

broad overlap of the two groups as is evident from inspection of the ranges of values in Tables 3 and 4. The smallest overlap existed in time periods of from 4 to 15 minutes inclusive. In fact during this interval the control mean minus two standard deviations was lower than the coronary mean minus one standard deviation with the result that only 2.27 per cent of the controls but 16 per cent of the coronary heart disease group fell below this point.

The continual drift to negative values was common to both groups (Figure 2). Since the two groups started at approximately the same level and since the coronary heart disease group was much lower than the control group at 30 minutes it follows that the overall rate of change was greater in the coronary heart disease group.

The total change during the 4 to 15 minute time interval was computed for each individual and the frequency distribution of this value was drawn for the coronary heart disease group and the control group. Both distributions were markedly asymmetrical but the healthy control group was concentrated at smaller total changes (50 to 100 millivolts) whereas the coronary heart disease group showed no marked concentrations and in general showed greater changes.

Interpretation of findings

How can the gross differences between the reducing intensities of the two groups as evidenced by the mean values of the oxidation reduction potentials be explained? The overall rate of change in activity was faster in the coronary heart disease group. Such changes may be the result of absolute differences in concentration of various inorganic ions and/or combination of enzymes or coenzymes together with accelerators or inhibitors that may be present in the saliva.

Van Potter (1949) has listed the following eight variables responsible for the *in vitro* control of enzyme activity: temperature, pH, substrate concentration, co factor concentration, product concentration, inhibitor concentration, oxidation reduction potential and ionic strength. Certain of these variables may be excluded from our consideration. The temperature in these experiments remained at 22 ± 1.5 degrees centigrade thus the possible differences due to temperature are negligible. The range of pH values of various

salivas tested was between 6.3 and 7.8 and while this may make some difference in the individual instance it was thought unlikely, because of the excellent buffering capacity of saliva that changes in pH produced the observed changes for the duration of these procedures.

It has been shown that the coronary heart disease group differed from the control group in physique and in several biochemical properties. When the physique and other factors were controlled through the use of the matched pair technique, the biochemical differences still existed. The present chapter confirms the observations made in the previous studies that showed a basic biochemical difference between the two groups and is perhaps, more definitive in that the approach may involve basic enzyme systems.

Using as the statistical lower limit of normality the conventional two standard deviations below the mean of the control group it was found that 16 per cent of the coronary heart disease group and only 2.27 per cent of the control group fell below this level in the 4 to 15 minute time interval. Accordingly it was felt that apparently normal individuals whose salivary oxidation reduction potentials at 4, 5, 10, and 15 minutes fall below $+48.5 \pm 0.5$ — 222.5 and — 360.5 millivolts respectively may show other characteristics of the coronary heart disease group and merit further study.

Since the magnitude of the differences shown to exist in the salivary oxidation reduction patterns are of the same order as some of the other biological attributes of coronary heart disease this phenomenon may perhaps be considered to be as meaningful as the other biological attributes in distinguishing the person with coronary heart disease. More concentrated study is indicated in order to isolate the differences in specific enzyme systems or inorganic ions of both groups of individuals.

It should be emphasized that the reproducible phenomenon of oxidation reduction potentials of saliva cannot be explained satisfactorily with the evidence at hand. No attempt is made here to explain it in terms of specific oxidation reduction systems or other phenomena which are known to affect these potentials. However that there is a difference in these potentials of saliva between the coronary heart disease group and a healthy control group is apparent from the changes that occur in the potentiometer readings of saliva under the conditions described herein.

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CHAPTER XII

Summary and Conclusions

THIS monograph presents the findings of a three year research program on coronary heart disease in young adults conducted at the Massachusetts General Hospital in the search for significant etiological clues. The study represents the combined efforts of many individuals on diverse aspects of this disease entity. In addition to 100 coronary heart disease patients under the age of 40 who had experienced myocardial infarction (at least six months prior to admission for the minimal 24 hour study), there were 146 unmatched controls. A group of matched controls for the 97 male patients was also made up consisting of 74 men from the unmatched control group and 23 additional men.

Clinical Appraisal

It is noteworthy that the clinical findings were not impressive. Several items do, however, merit attention. Only 5 patients (5 per cent) had arcus senilis; this incidence is much lower than that reported by certain other investigators (Boas, 1949), but it is in keeping with other observations of our own (Gertler and Garn, 1950). Cardiac arrhythmias consisting of premature contractions only were observed in but 1 instance. Paradoxical pulsations or diminished apical pulsations were observed in only 10 cases, a much lower incidence than that reported elsewhere (Dack et al., 1940; Garland and Thomas, 1948). Another interesting clinical impression was that as a group the patients appeared about 10 years older than their chronological age.

Although the coronary patients consumed some forms of alcohol and used tobacco in statistically larger amounts than the control group, the findings do not warrant any conclusions as to a causal relation between the use of alcohol or tobacco and coronary heart disease.

Family Incidence

Heredity

The study of hereditary factors in coronary heart disease has disclosed several interesting facts. The strong influence of heredity on coronary heart disease cannot be denied but the mode of gene transference or inheritance and the degree of penetrance have not been clarified by this study.

The study of parental mortality revealed that at the time of the last interview 61 per cent of the parents of the unmatched control group were alive in contrast to 47 per cent of the parents of the coronary heart disease group. Fifty eight per cent of the mothers and 35 per cent of the fathers of the coronary heart disease group were alive as compared with 73 per cent of the mothers and 48 per cent of the fathers of the control group. Age difference in the parents was shown not to be the cause of this differential mortality.

It is noteworthy that proportionately more parents of the coronary heart disease group than of the control group died of cardiovascular disorders. 51.3 per cent of the deceased mothers and 64.4 per cent of the deceased fathers of the coronary heart disease group as against only 35.9 per cent of the deceased mothers and 46.2 per cent of the deceased fathers of the control group.

There were more deaths due to coronary heart disease in the families of the coronary heart disease group than in those of the control group. Thus 9.8 per cent, 37.1 per cent and 8.1 per cent of the mothers, fathers and siblings respectively of the coronary heart disease patients died from coronary heart disease in contrast to 7.7 per cent, 18.5 per cent and 1.0 per cent respectively of the mothers, fathers and siblings of the control group.

Race

Ethnic origin as an original factor in coronary heart disease was also considered in this study. There were 27 patients of Jewish origin (26 men and 1 woman). 15 were strictly "old Americans", 19 were various British Isles mixtures, 12 were pure Irish, 6 were pure English and 2 were Negroes. The predominance of Jews in this series is in keeping with the observations of other investigators; the reason for it however is not clear. It is known that Jews are particularly prone to diseases involving abnormal lipid metabolism such as Tay Sachs disease, Gaucher's disease and Niemann

Pick's disease This high incidence may in part be due to the high degree of endogamy in Jews Whether these observations may be extended to coronary heart disease cannot be answered by this research

Physique and Morphological Characteristics

The coronary heart disease group differed in certain special morphological characteristics from the control group These by and large with the exception of genital size (which is larger in the coronary heart disease group) may be attributed to the presence of mesomorphy (texture and a lower waist hip index) and a paucity of ectomorphy (less thigh interspace less knee interspace and more hip roundness)

There were significant differences between the coronary heart disease group and the control group in certain anthropometric measurements Generally the coronary heart disease group showed a decrease in vertical measurements an increase in horizontal measurements and an increase in depth measurements as contrasted with the control group The differing measurements may be summarized as follows (a) vertical—stature span total face length, hand length and chest length (b) horizontal—hand breadth and nose breadth (c) depth—upper chest depth and total chest depth One should be cautioned however not to define a 'typical coronary heart disease patient from anthropometric measurements alone

The somatotype findings in this study are illuminating and add greatly to our understanding of those further phenotypic expressions which are assessable only by biochemical analysis Hence the somatotype is invaluable if employed as a frame of reference to relate and correlate the biochemical findings (see below, Biochemical Findings) The concept of such biochemical characteristics as a chemotype is another step in the definition of the normal physique its implications in disease have been discussed (Gertler, 1950) The coronary heart disease patients as a group were 44 per cent dominant mesomorphs and 6 per cent dominant ectomorphs as compared with the controls who were 22 per cent dominant mesomorphs and 18 per cent dominant ectomorphs It is noteworthy that the coronary mesomorphs were mainly *endomorphs* mesomorphs while the few coronary ectomorphs were *mesomorphs* ectomorphs

The finding that the young coronary heart disease patient is

usually an endomorphic mesomorph permits certain corollary observations and conclusions since the endomorphic mesomorph behaves differently physiologically and psychologically from other mesomorphs and other somatotypes (Sheldon 1940) Mesomorphs generally appear prematurely aged owing in part to their coarse heavy wrinkling Thus the clinical observation that the young coronary heart disease patients appear one decade older may be due in part to the normal older appearance of mesomorphy This tenet is reinforced by the observation that mesomorphs reach puberty 1 to 1 1/2 years earlier than individuals with other somatotypes Accordingly it is reasonable to suggest that mesomorphs at all ages are physically 10 per cent older than their chronological age (assuming that puberty occurs at 12 to 14 years)

According to published data there are a selected group of temperament traits and occupations which are associated with coronary heart disease The coronary patient is described as being a hard driving goal directed individual whose monodirective personality suggests refuge in work (Dunbar 1943) Some investigators have intimated that there is an excess of executive managerial and planning personnel in the young coronary heart disease group (Boas 1949) while still others have suggested a causal relation between occupation and coronary heart disease (Master et al 1939) Several questions may be raised on the merits of such a rigid classification and categorization Most reports on coronary heart disease come from urban centers where doctors are more accessible for any acute illness Accordingly, the medical records are apt to be influenced because (a) better records of patients are available to organized study groups and (b) few farmers or rural employed individuals are likely to be available to the urban physician and hence their medical records are rarely available for an organized study group and are likely to be excluded from any statistical analysis of coronary heart disease

If one employs the psychological and occupational correlates of mesomorphy adopted by Sheldon (1940) Hooton (1945) Seltzer (1945) Morris (1948) Fiske (1944) and Garn and Gertler (1950) one is impressed by the fact that many of the aforementioned descriptions of the young patient with coronary heart disease could easily fit the mesomorph The mesomorph enjoys participation in dangerous and strenuous undertakings he loves

speed he is hard driving and goal directed. All these characteristics may account for the non conventional behavior pattern in the formative years of the coronary heart disease patients. The mesomorph has a deep desire to be important in this world and to wield power over other beings and environment. Such a trait may assume many garments of ambition such as those of executives, managers, army officers and the like. Finally the striking preponderance in athletic ability is not surprising in the coronary heart disease group for there can be little athletic prowess in an individual who is not well endowed with the mesomorphic component.

Athletic Activity and Occupations

The investigation of the relation of athletics and occupations to coronary heart disease yielded interesting information. The coronary group scored higher in their athletic ratings than did comparable controls. This fact might well be attributed to mesomorphy for it has been established that athletic prowess requires at least a rating of 5 in mesomorphy (highest rating possible is 7). It cannot be stated therefore that athletic participation is causally related to coronary heart disease for the presence of excess mesomorphy is merely the common denominator to the two characteristics, namely, athletics and coronary heart disease. The study of occupations as related to the disease revealed a preponderance referred to above of individuals (42 per cent) in the managerial capacity. Again it cannot be stated with certainty whether the risks, mental strain and preoccupation of individuals in managerial positions are responsible for coronary heart disease or whether the ambitious driving nature which culminates in a managerial post is actually an additional causative factor.

Masculinity

The question of masculinity in coronary heart disease has been considered at great length. Several older observations have been confirmed, several clinical impressions have been analyzed and quantified, others have been refuted and still others have been modified. The ratio of 96 men to 4 women observed in a study of 100 cases of coronary heart disease under the age of 40 years by Glendy et al (1935) was essentially unchanged for in the present series of 100 cases there were 97 men and 3 women. Thus the pre

dominant male element in this disease group under the age of 40 is the outstanding etiological clue. The robust young male (White 1944) has been delineated as a male whose physical structure is that of an endomorphic mesomorph—a heavily built bony muscular and sturdy male. A final appraisal of young males apparently most masculine will necessarily be postponed until further studies have been made. Suffice it to say that these men were not psychologically the most masculine according to the Terman Miles test; the coronary heart disease patients were less masculine in their final scores than the matched control group. The coronary group actually achieved scores which were comparable to those of men ten years their senior, and this according to Terman and Miles would indicate a trend toward the typically feminine, for as men become older their scores tend to assume the distribution usually ascribed to high feminine scores.

At first it appears paradoxical that the coronary group as a whole appeared to be the most masculine according to physical attributes such as body build and secondary morphological characteristics like hip roundness, thigh interspace, and hair distribution, and yet did not appear to be highly masculine according to psychological appraisal. It should be emphasized, however, that the physical and psychological aspects of masculinity are insignificantly related to each other. As measured by the Terman Miles test, psychological masculinity and femininity represent a composite of attitudes which stem from heredity, social background, and acculturation during life. One must always keep in mind that the scores achieved by the coronary heart disease group could have been modified by (a) education and/or cultural level of the group and (b) the experience of being ill. Accordingly, the scores reported herein must be evaluated with some reservation at this juncture.

It had been suggested from clinical observations that the young coronary heart disease patient is grayer, balding, and more hirsute in regions other than the scalp. There proved to be no evidence, however, of increased graying in the coronary heart disease group; frontal, tonsorial, and combined balding showed no significant difference from that in the control group. There was no evidence, furthermore, of a significantly greater amount of body hair in the coronary heart disease group as compared with the control group. The study did not concentrate on the relations of androgens to

hirsutism and no conclusions on this point may be drawn from the findings

The relation of urinary androgen excretion to masculinity has been studied by a number of investigators and has given rise to a great deal of speculation. The evidence of lower sterone excretion in the 17 ketosteroid urinary studies cannot be interpreted as meaning 'less masculinity' in the coronary heart disease group for (a) the lowered sterone excretion may be a result of the myocardial infarction, and (b) there is no definitive evidence that the urinary sterone excretion is associated or correlated with masculinity.

Endocrine Findings

Endocrine studies were limited to a thyroid and a testicular-adrenal survey based on 24 hour urinary sterone excretion. The thyroid status was particularly studied in this young coronary heart disease group because of the possible influence of the thyroid on the course of coronary heart disease either through a causal relation with the abnormal blood lipids or through other unknown metabolic factors. After studying thyroid influences with the aid of (a) basal metabolic rates (b) radioactive iodine uptake and (c) blood lipids it was concluded that there appeared to be a slight alteration in the thyroid activity from the euthyroid state in the direction of hypothyroidism. Again it is not known whether this is a post hoc or a propter hoc phenomenon.

The procedure of basing the testicular-adrenal survey on the 24 hour urinary 17 ketosteroid (sterone) excretion is admittedly crude for it does not differentiate between secretions of the two glands but any alteration would be of interest as a point of reference. There was however essentially no difference between the means of the daily urinary sterone excretion in the coronary heart disease group and in the control group. Nevertheless certain findings are noteworthy. There were fewer individuals in the coronary heart disease group whose daily urinary sterone value exceeded 14 mg. while twice as many (17 per cent) of the coronary heart disease patients excreted less than 6 mg. of sterone daily in their urine. Furthermore the coronary heart disease patients who later died showed significantly lower daily urinary sterone excretions than either the rest of the coronary group or the unmatched control group.

Biochemical Findings

The biochemical findings are to be evaluated in two ways first as etiological factors in coronary heart disease and second in relation to the somatotype findings

Cholesterol

The question of the causal relation between the level of total cholesterol in the serum and coronary heart disease was restudied and re evaluated. The mean levels of serum total cholesterol in the coronary heart disease group the matched control group and the unmatched control group were 286.5 ± 6.6 , 241.9 ± 5.5 and 224 ± 3.5 mg per cent respectively. While the mean values are significantly different the distribution curves are markedly continuous. From this observation it is reasonable to infer that a threshold level of serum total cholesterol for coronary heart disease does not exist and that additional factors probably play a role.

Lipid phosphorus and cholesterol/lipid phosphorus ratio

One of these additional factors appears to be the serum phospholipids. The relation of the serum total cholesterol to the serum phospholipids seems to be an important factor in the etiology of coronary heart disease. When the ratio of total cholesterol to lipid phosphorus was being studied it was found that in the coronary heart disease group the matched control group and the unmatched control group the mean values of the ratios were 22.4 ± 5 , 19.4 ± 3 and 18.7 ± 2 respectively. In view of the increasing evidence that the colloidal stability of the cholesterol in the serum is dependent partially upon the ratio of total cholesterol to lipid phosphorus it was considered that this ratio had greater meaning in studying coronary heart disease than either of the components considered separately. An additional confirmation of this hypothesis arose by deduction from the study of age changes and serum lipids. It was revealed that both serum total cholesterol and serum phospholipids rise with age in both the coronary heart disease group and the control group. However on analysis by the technique of partial correlations it was shown that when the influence of the phospholipids is removed in both groups the correlation between age and cholesterol disappears. Moreover when the influence of cholesterol is removed the phospholipids continue to show a

correlation with age in the normal group but do not keep pace with age in the coronary heart disease group. Thus a fundamental difference may exist in the two groups namely that in the coronary heart disease group cholesterol deposition in the intima may be enhanced by the lack of a colloidal stabilizer which may be due to a failure of the phospholipids to rise with age and hence to alter the total cholesterol/lipid phosphorus ratio.

Uric acid

The question of the level of uric acid in the serum was considered. It was found that the average value of serum uric acid in the coronary heart disease group was 5.13 ± 1.2 mg per cent in the matched controls 4.85 ± 0.7 mg per cent and in the unmatched controls 4.64 ± 0.6 mg per cent. The differences between the averages of the coronary group and the two control groups were statistically significant. It is of further interest that 22 per cent of the coronary heart disease group showed serum uric acid above 6.0 mg per cent while only 6 per cent of the unmatched control group showed serum uric acid above that level.

Biochemical morphological relations

How do these chemical findings fit in with the concept of the morphological structure of coronary heart disease patients presented in this study? It will be recalled that the individual most likely to experience a myocardial infarction prior to the age of 40 is structurally an endomorphic mesomorph. In relating variations in the levels of serum total cholesterol and serum uric acid to variations in physical structure several patterns were observed in the two groups.

In the control group the highest absolute levels of cholesterol and uric acid were associated with the endomorphic physique and the lowest levels were associated with the ectomorphic physique. The differences were statistically significant. There was no significant difference between the endomorphic and mesomorphic physiques in respect to these levels.

In the coronary heart disease group however two important changes were observed.

- 1 The level of serum uric acid increased significantly over the control level in only one physique the endomorphic.

- 2 On the other hand the level of serum total cholesterol increased over the control level in each physique reaching its highest value in the coronary mesomorph in contrast to the lowest value in the control ectomorph

These two observations confirm and emphasize the original data on somatotypes. The levels of serum total cholesterol and serum uric acid have their highest correlation with the mesomorphic and endomorphic dominances that are most typical of young adult coronary heart disease patients. Accordingly it is reasonable to suggest that a metabolic relation is involved that is a tendency toward more frequent alteration in the metabolism of these two biochemical factors in the mesomorphic and endomorphic physiques.

Diet

The question whether dietary factors are causally related to coronary heart disease was investigated by studying the weekly ingestion of foods containing cholesterol and the relation of the ingested cholesterol to the cholesterol level in the serum of both the coronary heart disease and the control groups. It was found that the patients with myocardial infarction had ingested on the average 3.3 ± 1.5 gm and the control group 3.9 ± 1.2 gm of cholesterol weekly. It will be recalled that the average levels of serum total cholesterol for the coronary heart disease group and the control group were 286 mg per cent and 224 mg per cent respectively. Thus the coronary heart disease group ingested less cholesterol than the control group but possessed more cholesterol in the serum. It appears that the endogenous source of cholesterol plays a definite role in the etiology of coronary heart disease.

Oxidation Reduction Potentials of Saliva

The study of saliva revealed several interesting phenomena. The coronary heart disease group in contrast to the matched control group showed a faster rate of change per minute during the entire test procedure which lasted for 30 minutes but this was particularly noticed during the interval between the 4 minute testing and the 15 minute testing. The average potentiometer readings of the coronary heart disease group at 4 minutes 5 minutes 10 minutes and 15 minutes were $+157 \pm 13.9$ $+133.5 \pm 16.7$ $+0.5 \pm 28.8$ and -98.5 ± 33.8 millivolts respectively. These

values are statistically lower than those observed in the control group which were $+195.0 \pm 8.1$, $+171.5 \pm 9.2$, $+93.5 \pm 16.5$, and $+23.5 \pm 22.7$ millivolts for the 4 minute 5 minute 10 minute, and 15 minute time intervals respectively

Conclusions

A great deal has been achieved with modern methods in the diagnosis of the acute or subacute phase of coronary heart disease which terminates in myocardial infarction. However, the increasing death toll from coronary heart disease suggests that still another form of approach to the problem should be studied namely prevention. It is obvious that before preventive measures are instituted recognition of the individual most prone to coronary heart disease will be necessary. Efforts should be made to determine which individuals have the greatest tendencies to myocardial infarction. How can we recognize these presumably abnormal people in the entire population?

The ability to prevent disease is generally proportional to the knowledge of the etiological factors and pathogenesis of a disease. It is for these reasons that the problem of preselection of men prone to coronary heart disease from presumably normal males has been difficult in the past. However in this study of persons who had experienced a myocardial infarction prior to the age of 40 certain leads were uncovered which may prove helpful in the recognition of those in whom myocardial infarction is most likely to occur.

The suggested techniques are based upon evidence accumulated in this study which bears out the original thesis of the Coronary Research Project that coronary heart disease is caused not by one etiological agent but by many factors. The multidisciplinary nature of the study has been most useful in that it has made it possible to select those characteristics which occur in the highest degree in coronary heart disease patients and to recognize them as potentially dangerous to any individual who possesses them (see Gertler et al 1951). By taking into consideration sex body build morphological characteristics heredity serum total cholesterol serum uric acid serum total cholesterol/serum lipid phosphorus ratio CUP index and salivary redox potential it should theoretically be possible to preselect coronary prone individuals from the population. Since the

interrelations of many factors are involved in this method it probably has more merit than reliance on any single factor. A long follow up study of the control groups should give us more evidence.

It is hoped that as a result of the advances in preselection it may be possible in the near future to institute some form of preventive therapy to delay the episode of coronary attack. At present there is to our knowledge no definite form of replacement or adjuvant therapy which has proved to be effective in this respect. The difficulty stems partially from inadequate understanding of coronary heart disease and partially from lack of concerted effort in this aspect of preventive medicine. We hope that clues to the solution of these two important problems will soon be found.

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APPENDIX A

Terman Miles Masculinity Femininity Test

THE Terman Miles test was one of the tools used in the assessment of masculinity in this study. The following excerpts are taken from the book *Sex and Personality* by Lewis M. Terman and Catharine Cox Miles* to aid the reader in evaluating the test.

Exercise 1 Quadruple choice Word Association

the subject's task in Exercise 1 is to underline that one of the four given associates following a stimulus word which seems to go best with the latter. Each form of the M-F test contains 60 stimulus words making 120 in all.

In this and all the other exercises with the exception of Exercise 3 the present study of sex temperaments is based upon the weighted scores of the individual items which are given in Appendix IV [of Terman and Miles book]. The weighted scores were used rather than unit scores in order that magnitude as well as direction of the sex differences could be taken into account.

The population groups used in the derivation of weights for Exercise 1 included roughly 125 pupils of each sex in grade seven, 100 of each sex in the junior year of high school and 50 college students of each sex in all about 550 subjects. These are the subjects who furnish the data for our sex comparisons on Exercise 1.

For purposes of convenience and also because they appeared more promising of results the responses to Exercises 3, 4, and 5 were examined before those to Exercises 1 and 2. When Exercise 1 was taken up a number of hypotheses had already been reached with regard to the nature of some of the more important psychological differences between the sexes. These hypotheses based upon an

By permission from *Sex and Personality* by Lewis M. Terman and Catharine Cox Miles. Copyright 1936 McGraw-Hill Book Co. Inc. New York. Pp. 373-374. 380-381, 384, 390, 416, 434, 438, 443-450.

examination of the responses of male and female groups to Exercises 3 to 5 were utilized as a basis for forecasting the sex preferences of associations in Exercise 1. It will be interesting to see how adequately the explanatory hypotheses empirically arrived at from the responses in certain exercises explain the sex differences in exercises of a very different type.

Exercise 2 Ink blot Association

In each form of the M F test 18 ink blots or drawings are presented and the subject is asked to underline one of the four words following each (the word that tells what the drawing makes you think of most)

The populations used in the analysis of responses to Exercise 2 were the same as for Exercise 1. We have tabulated the responses of the subjects in two ways: one the less illuminative taking the associations absolutely; the other by considering the more sharply contrasted associations in relation to one another and to the stimulus object. The first tabulation which is self explanatory serves the former purpose.

Exercise 3 Information Test

Each form of this exercise consists of 70 sentences (i.e. 140 in all) to be completed by underlining that word out of four supplied that gives the correct information required. It is a quadruple choice information completion exercise: success in which calls primarily for knowledge of fact and would seem therefore to depend upon the experience and interests of the subject. Responses were analyzed for the same populations as in the case of the two previous exercises.

We shall briefly summarize the results of our scrutiny before considering the detail.

Within the range of the 140 items set and the subjects who responded to them a comparison of the sex preference scores indicates that

- 1 Females show more knowledge
 - (a) About domestic occupations
 - (b) About matters of personal or household decoration, adornment and etiquette
 - (c) About literature (fiction), music (or rather musical technique) and conventional taste in colors

(d) Where the topic is one that appeals to one's active sympathy or feelings of tenderness (including in particular the maternal emotions)

2 Males show more knowledge

(a) Of extradomestic facts and events political social economic and business

(b) Of physical and scientific facts

(c) Of exploit adventure invention whether in fact or fiction

(d) Where the topic is one that appeals to the pugnacious aggressive or vigorously active tendencies

Exercise 4 Emotional and Ethical Response

Exercise 4 falls into six sections of which four concern occasions of anger fear disgust and pity respectively the fifth considers occasions of moral reprobation and the last compares preferences for alternative situations or types of occupation The analysis of Exercise 4 was based upon data from the following populations 148 boys and 172 girls in the seventh grade 116 boys and 128 girls in the junior year of high school and 50 college students of each sex in all 664 subjects

Exercise 5 Interests Likes and Dislikes

Exercise 5 is divided into eight series of likes and dislikes in the first five of which the subject has to declare whether he likes dislikes or is indifferent to

A Vocational occupations

B People with certain characteristics

C and D Certain forms of pastime entertainment occupations or situations

E Certain books

The last three series ask him which items from a given program he would like dislike or neither like nor dislike

F To draw (if an artist)

G To report on (if a newspaper reporter)

H To do or visit (if on a period of travel)

If the information exercise is an indirect this one is a direct inquiry into individual interests and to that extent would appear to obtain its results less from the accidents of experience and more

from the emotional dispositions of the subject and so to reflect more directly his actual temperament and personal habits of mind. By actual we do not necessarily mean innate for our likes and dislikes are also influenced by environment.

Our discussion is based upon data from 158 subjects in the grade school 200 in high school 52 in college and 80 non-academic adults 590 in all. Each group has an equal number of males and females.

Exercise 6: Personages and Opinions

This exercise has two sections: one calling for expression of attitude toward selected historical personages; the other for judgment of truth or falsity of certain statements. Responses to both sections were analyzed for the following subjects: 121 boys and 122 girls in the seventh grade; 102 boys and 118 girls in high school; and 50 men and 50 women in Stanford University; a total of 563.

Exercise 7: Introvertive Response

The exercise contains 42 questions in each form with Yes or No answers on tastes, habits, emotional and imaginative tendencies, facts of experience, and a few other topics, many of the answers demanding self-scrutiny. In general they are of the type commonly used in tests of introversion or neurotic tendency. The subjects were the same as for Exercise 6 except that the number of high school girls was 102 instead of 118.

We may arrive at an index of preference (for an affirmative answer) by adding the figures under Yes and No and attaching to the sum the sign under Yes, since the weights for Yes and No responses are nearly always the same and never differ by more than 1, e.g.

Do people ever say you talk
too much? + 2 Yes — 1 No gives a P I + 3 (male)
"Are you happy most of the
time? — 3 Yes + 3 No gives a P I — 6 (female)

SUMMARY AND CONCLUSIONS OF TESTS

Before concluding this inquiry with a brief discussion of the outcome it is desirable even at the risk of seeming tiresomely

repetitive to recapitulate its main findings exercise by exercise for their strength rests upon cumulative evidence rather than upon any single decisive experiment Taken serially they run as follows

Exercise 1 Word Association

1 If we take the associated words absolutely females pick more often than males upon terms for domestic things or things suggestive of kindly or sympathetic activities and much more often upon terms for articles or qualities of adornment and for colors males more often upon scientific and business terms and particularly upon terms suggestive of excitement and adventure and upon words for foods and each sex prefers names of persons of its own sex

2 If we take the items which show the most sex-contrasted responses divergences follow the same lines and also indicate a male preference for words signifying machinery common tools and outdoor pursuits

Exercise 2 Ink blot Association

3 Response words most obviously associated with machinery or science and with outdoor activities and adventure are picked upon more often by males more of those connected with domestic occupations and with aesthetic experience or personal adornment by females

4 When we consider the items which show the most sex contrasted responses the term which the stimulus figure evokes is in almost every case one connected with a common occupation distinctive of the responding sex

Exercise 3 Information

5 Females are more correctly informed about domestic occupations domestic and individual embellishment etiquette fictional literature certain points of musical technique color shades and differences and on topics that appeal to active sympathy and maternal interest Males are more correctly informed about political business economic scientific and physical facts about exploits adventures and inventions and on topics that evoke aggressive and active bodily propensities

6 This divergence between the sexes is most marked in knowl

edge of facts or events that interest aggressive or adventurous dispositions on the one hand and maternally tender or sympathetic dispositions on the other

Exercise 4 Emotional and Ethical Response

7 Females express the most distinctive degree of anger on occasions of very unsympathetic or cruel treatment of human beings where help or sympathy is meet

8 Females tend to show a more distinctive degree of anger over school offenses and social vexations than over business and extra domestic troubles

9 The sexes diverge more in the fear than in the anger responses

10 Within the set of fear inspiring objects and situations presented the more fearsome the object the greater the female distinctive fear

11 Females express more disgust than males in general but particularly at disgusting male practices (repugnant habits of dress and person) at coarse language and at sexual immorality

12 Females express in general more pity than males but most for the weak helpless and visibly distressed especially where the object is a human being or a creature attractive in appearance and for cases of female more than of male distress

13 Females are in general more condemnatory than males but more noticeably in petty offenses and in offenses more common in males In negligible offenses on the one hand and very serious offenses on the other the sex distinction is inconsiderable

14 The severity of male censure increases more than that of female censure with increased gravity of the offense

15 Of the alternative occupations and objects presented for choice in the last section of the exercise males distinctively prefer the out of door and adventurous and the useful rather than the decorative females prefer indoor and urban conditions of living and things attractive in appearance rather than the useful

16 Females express more liking for working with men than men for working with women

17 Females tend to express a higher degree of the four emotions (particularly of disgust) and of moral censure than males

express but proportionately less in moral censure and anger than in pity fear and disgust

18 In general males record more defect of emotion and of moral censure than females particularly of disgust and fear with pity moral censure and anger following in that order

19 The interval between female excess and male defect averages greatest with disgust least with anger and moral censure

Exercise 5 Interests

20 The occupations for which females express a distinctive preference are the indoor artistic and decorative and the directly ministrative distinctively preferred by males are those entailing adventure bodily risk and muscular strength or prolonged exertion

21 Males distinctively prefer occupations undertaken predominantly by males females like male as well as female occupations

22 Females record a higher distinctive preference for predominantly female occupations than males for predominantly male occupations but also on the whole as high a preference for mixed occupations as males for male occupations

23 Throughout Sections *B* to *H* of this exercise a sex tends to prefer objects or topics which more particularly engage or concern members of that sex

24 Among the various types of material presented for response in Sections *B* to *H* males are found to express distinctive preference for experience implying adventure aggressiveness or interest in mechanical contrivances for out of door and physically strenuous occupations and for business commercial and political interests Females express preference for experiences evoking maternal tenderness or active sympathy and for aesthetic and domestically social experiences

25 In the aggregate female likes considerably exceed male likes and male dislikes exceed female dislikes but this holds of some sections more than of others In three sections of one form male exceed female preferences

26 In the aggregate male neutral scores (neither like nor dislike) exceed female considerably but (with one exception) this excess is confined to those sections in which female likes are most distinctive

Exercise 6 Personalities and Opinions

27 Females show ■ distinctive preference for women unfortunate people and philanthropists males for successful generals sports heroes and defiers of convention

28 Females distinctively believe statements favorable and disbelieve statements unfavorable to the female sex they subscribe to kindly males to rougher sentiments

Exercise 7 Introvertive Response

29 Males affirm distinctively tastes and habits that involve adventure or courage females habits or experiences that imply timidity active sympathy and care for personal appearance and with one or two exceptions they more readily confess weaknesses in emotional control and (less noticeably) of physique Females also admit more psychic abnormalities

30 Females more often than males give the introvertive type of response

We may now consider two questions to which the present findings give rise (1) Can we extract from them a single prime principle of sex difference at once not too vague to be ambiguous and not so particular as to be insignificant? (2) What so far as our evidence goes appears to be the relation of the differences we have enumerated to nature and nurture to endowment and environment? We shall take these questions in succession

1 Is there one dominant principle?

It is obvious that from whatever point we have started whether from the knowledge shown by the sexes or from their associations or their likes and dislikes for people vocations pastimes books or objects of travel or whether we have explored directly or devotously their emotions tastes opinions and inner experiences we have found ourselves arriving at much the same conclusions—all our ways have led to Rome But the final scene has two aspects—two sides of the same picture—one showing differences in the direction of interest the other differences in the direction of emotions and impulses

From whatever angle we have examined them the males included in the standardization groups evinced a distinctive interest in exploit and adventure in outdoor and physically strenuous

occupations in machinery and tools in science physical phenomena and inventions and from rather occasional evidence in business and commerce. On the other hand the females of our groups have evinced a distinctive interest in domestic affairs and in aesthetic objects and occupations they have distinctively preferred more sedentary and indoor occupations and occupations more directly ministrative particularly to the young the helpless the distressed. Supporting and supplementing these are the more subjective differences—those in emotional disposition and direction. The males directly or indirectly manifest the greater self assertion and aggressiveness they express more hardihood and fearlessness and more roughness of manners language and sentiments. The females express themselves as more compassionate and sympathetic more timid more fastidious and aesthetically sensitive more emotional in general (or at least more expressive of the four emotions considered) severer moralists yet admit in themselves more weaknesses in emotional control and (less noticeably) in physique.

But we must define some of our terms more precisely for instance aggressiveness and self assertion. The evidence is for initiative enterprise vigorous activity outdoor adventure aggressiveness need not imply selfishness or tyranny or unfair attack. The compassion and sympathy of the female again appears from the evidence personal rather than abstract less a principled humanitarianism than an active sympathy for palpable misfortune or distress. In disgust in aesthetic judgment and in moral censure the evidence is rather for the influence of fashion and of feeling than of principle or reason. Our evidence need not imply the possession of a truer taste or a more discerning conscience.

But in asking how deep these sex distinctions go we reach our second question. *What appears to be the relation of our main sex difference to nature and nurture to endowment and environment?*

The question is not let us remind ourselves whether this or that trait is innate or acquired for every human act or thought is both but whether the actual sex differences we are discovering are ascribable to biological (genetic) factors dividing the sexes or to sex differences in their training and environment. So far as the evidence of our experiment goes we are not justified in ascribing the manifest differences to one alternative exclusively. Certainly we do not have enough evidence to exclude the gross physiological

differences between the sexes from any part in determining the distinctive preference of the male for heavy muscular work and of the female for less active occupations or in determining her greater sympathy for the young and weak or her greater interest in home life with the relegation of outside interests to the male. To actual or anticipated childbearing and motherhood—differences physiologically determined—we have found no reason to deny a part in determining differences in overt habits and emotional dispositions. And in the present state of our ignorance it would be even more rash to deny the possible influence upon sex temperaments of the manifold differences between the sexes in their endocrine equipment and functioning.

Whatever our view as to the innateness of the distinctive tendencies at least as to maternal tenderness in the one sex and comparative aggressiveness in the other our experimental evidence is inconclusive. However when we examine the more direct manifestations of these and other contrasting tendencies in our exercises and consider how any particular manifestation comes about the power and reach of what we have named cultural sex bias its many plain and subtle effects on the upbringing and environment of the sexes within the groups we are considering keep coming to one's mind. In so many ways too familiar to realize each sex gives and receives such different treatment as largely to explain the divergencies in expression or in fact revealed by the material we have studied. Singularly powerful in shaping our development are other people's expectations of us past and present as shown by their practice and their precept. Whether the boy is innately more aggressive and fearless more handy with the electric lighting than with the cooking stove more interested and informed about public affairs and about science more active and enterprising physically and whether the girl is by nature more sympathetic gentle timid fastidious more attracted to pots and pans than to rods and guns more punctilious in dress personal appearance manners and language at any rate society in the shape of parents teachers and one's own fellows of whichever sex expects these differences between the sexes and literature reflects them. Irresistibly each sex plays the role assigned even in spite of its own protests. The consequence is that throughout these several exercises however statistically consistent the distinctive sex responses may prove we cannot tell how

deep the difference lies—or how the deeper and shallower factors combine. And here we must be content to leave the problem for it is clear that the deciding answer can be wrested not by a more meticulous struggle with this one set of exercises administered to groups comparatively homogeneous but from (1) parallel examinations of socially and racially different groups widely different in social tradition and circumstance, and (2) combined psychological and biological case studies of extreme deviants in sex temperaments within a given culture.

APPENDIX B

Heredity Record

HEREDITY histories of both coronary patients and controls were recorded on the accompanying form, which may be used in conjunction with a punch card system

MASSACHUSETTS GENERAL HOSPITAL
CORONARY PROJECT CARD 3

NAME _____

AGE AT ONSET _____ PRESENT AGE _____

BROTHERS AND SISTERS _____ BOYS _____

GIRLS _____ NO OF SONS _____ NO OF DAUGHTERS _____

AGE OF PARENTS

MOTHER (11 12) _____ FATHER (11 12) _____

MOTHER (14 15) _____ FATHER (14 15) _____

CAUSE OF DEATH OF MOTHER _____

FATHER _____

DECEASED BROTHERS OR SISTERS BROTHERS _____ SISTERS _____

CAUSE OF DEATH _____

HAVE ANY OTHER RELATIVES HAD HEART DISEASE _____

CORONARY HEART DISEASE _____

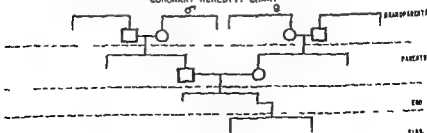
LIST ABOVE () with no death of th. m. death of th. m. 1st son 1st daughter 21 ()

NUMBER OF FATHER'S BROTHERS AND SISTERS _____

MOTHER'S BROTHERS AND SISTERS _____

DIRECTION: M to L from L to R for th. m. no 4 for only

CORONARY HEREDITY CHART



CONCLUSIONS _____

APPENDIX C

Summary of Heredity Data

KEY

○ FEMALE

☐ MALE

☐ or ☒ PROPOSITUS

☐ LIVING AT 32

☐ LIVING AT 32 ARTHRITIS

☐ Arth. = LIVING AT 32 (in parents and grandparents columns)

L 32 LIVING AT 32, ARTHRITIS (in parents and grandparents columns)

L 32 Arth LIVING AT 32

D 32 DIED AT 32

☐ D 32 DIED AT 32 CAUSE UNKNOWN

☐ D 32 DIED AT 32 PNEUMONIA

☐ D 32 DIED AT 32 PNEUMONIA (in parents and grandparents columns)

D 32 Pn DIED AT 32 ORDER OF BIRTH UNKNOWN

N O = NO ORDER OF BIRTH UNKNOWN

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

☒ CORONARY ARTERY DISEASE

Park PARKINSON'S DISEASE

PA PERNICIOUS ANEMIA

Pn PNEUMONIA

Ren RENAL DISEASES (glomerulonephritis)

RHD RHEUMATIC HEART DISEASE

TB TUBERCULOSIS

Typhd TYPHOID

Xanth XANTHOMATOSIS

Fist FISTULA

Gallib GALLBLADDER DISEASE

Hyc HYDROCEPHALY

Died DIED IN INFANCY

Diph Diphtheria

Scarlet Scarlet Fever

Infect Sep Infections

Mening Meningitis etc

Other than Cancer

Liver LIVER DISEASES

Lues LUES SYPHILIS

Acc ACCIDENTAL DEATH

Add ADDISON'S DISEASE

Arth ARTHRITIS

Asth ASTHMA

Cn.C CANCER

Ca. CHILD BIRTH

Db DIABETES

Epile EPILEPSY

016	D86	Pn	D	D80s	D84	D41	D70	D82	Acc	52
017	D49		D39	D71	Cs	D41	D70	D50		21
018	L73		D	D75		D52	D	D75		52
019	L56	Gallb	D33	D65		D60	Ren	D70		20
020	L62					L65				34
021	D72					D54				20
022	L72		D	D		D58		D		40
023	L65	Arth.	D62	Typhd	D40	L65	D70	D55		21
024	D59		D	D		D55		D		414
025	D49		D68	D68		L63	D72	D78		53
026	D36					L58	D90	D85		22
027	L68		D68	D38	TB	D65	D68	D75		41
028	D44		D75	D75		L59	D20sChB	D49	Acc	53
029	D38	Pn	D60s	D69	Ren	D64	D50s	D87	Cs	51
030	D38	Acc	D82	D87	Ren	D30	Acc	D70		20
031	L66		D	D		D64	D	D		43
032	L55					D47	Pn	D80		30
033	L69					D54				6
034	L68	Cs	D51	Asht	D89	Pn	D58	D60		25

NO	MOTHER	MOTHER'S MOTHER	MOTHER'S FATHER	FATHER	FATHER MOTHER	HER'S FATHER	PROPOSITUS & SIBLINGS
035	L86			D38			2 2
036	L65	D77	D72	L67	D60s	D70s	2 2
037	L63	D35	ChB	L65	D85	D40	4 0
038	D53			D62			4 2
039	L63	D86	D70	L64	D92	D49	4 1
040	D44	Ca		D48			3 2
041	D49	D61	D64	L69	D30s	D40s	6 0
042	D62			D36			2 2
043	D62	Ren		D53	Pn		2 1
044	D52	Pn	D88	L72		D90	2 3
045	D67	D70	Ca	D67		D60	4 1
046	L69	D76	D76	D76	D38	D40s	1 1
047	L54			D62			3 2
048	L71	Arth	D60	D53	Ca	D74	0 2
049	L64	Pay		D64	Lues		5
050	L54	Gallib		L55			5
051	L62			L65	D88		4 1
052	L75	Arth.	D81	Pn	D76		2 3
053	L57		D70	Gallib	D59		3 1

054	L 55	D 80 s	D 50 s	D 55	D 30 s Acc	D		21
055	L 65	D 40 Typ'd	D 42	L 72	D 72	D 74		11
056	D 80	D. Ch B	D 40 Ren	D 72	D 72	D 85		70
057	D 36			D 70 s Ca				210
058	L 75			D 59				30
059	L 69			D 59 Ca				13
060	L 58	D 70	D 62	D 62 Pn	D 70	D 70		211
061	L 74	D 60	D 70	D 80 s Pn	D 70	D 80		212
062	L 59	D 88	D 62	L 57	D 35 Ch B	D 69		7
063	L 75	D 70	D 80	D 67 Acc	D 80	D 80		7
064	D 38 Pn			D 58				41
065	D 53	D 64	D 73	D 56	L 83	D 60 s		32
066	D 65 Ca			D 68				110
067	L 66	D 30 Ren	D 60 s	D 60	D 60 s	D 83		35
068	L 68	D 55 Ren	D 68 Ren	D 84	D 87	D 70		10
069	L 57 Ren			L 67				40
070	L 75			L 77	D 83	D 84		12
071	D 52			L 86				31
072	L 63	D 20	D 70	D 68	D 30	D 30		53

NO	MOTHER	MOTHER'S MOTHER	MOTHER'S FATHER	FATHER	FATHER'S MOTHER	FATHER	FATHER'S FATHER	PROPOSITUS & SIBLINGS	♂♀
073	D63 ♂ ¹	D60 ○	D70	D50	D80	D50	D50	45 ^{Ph} 011 ⁵	21
074	D65 ♂			D55 Ph		D55	D50	4 ² 7 ⁹	32
075	L64	D82 Ca	D70s Acc	D40	L90s	D40	D60s	20 22 27 29	31
076	D72 ♂ ² ^{2b}			D80		D80		45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	44
077	L60	D32 Ch B	D71	L64	D80 ●	L64	D86	5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	52
078	L73	D73 ●	D60 Ren	D57 Ca	D60s	D57	D70	43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	52
079	D60 ♂ ¹ ^{2b}			D76		D76		43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	30
080	L59	D70 ○	D96	D49 Co	D65	D49	D99	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	20
081	L68 Db	D60 Ph	D72 Co	L67	D60 ●	L67	D45 Ph	18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	31
082	D72 ♂ ¹ ^{2b}			D65		D65	D80s	42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	53
083	L69			L71		L71		42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	14
084	L70 ○	D40 Ca	D78 Ca	D54	D69	D54	D78 Ph	47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	61
085	L58 ○	D83		L65	D42	L65	D62	42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	42
086	D50s			D60s Ph		D60s		42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	51
087	L62	D70s ●	D69	D55	D70s Ca	D55	D50s	42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	11
088	L65 ♂			D		D		42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	24
089	D45 ○	D58 Ca	D	L65	D43 Infect	L65		42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	12
090	L68 Db	D82	D39	L73	D75	L73	D75	42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	22
091	D51 ○	D60s ○	D65 Ph	L55	D60	L55	D70	42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	23
092	D70 ○	D70s	D60s	D84	D40s	D84	D84	42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	62
								42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	24

093	D 47	D 6	D 68	Pn	D 60s Infect	D 66 L 61 L 70s	D 80s Ren	D 80's Pn	3 2
094	L 61								2 0
095	D 35	☉							1 3
096	D 29	Pn							2 3
097	L 51	Gallb							3 0
098	L 55	☉							1 2
099	L 69								6 1
100	L 69	Arth							4 0

(Coronary Group—concluded)

UNMATCHED CONTROL GROUP

NO	MOTHER	MOTHER'S MOTHER	MOTHER'S FATHER	FATHER	FATHER'S MOTHER	FATHER'S FATHER	PROPOSITUS & SIBLINGS	♂
001	L 58	D 60	D 55	L 63	D 78	D 93	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	3 1
002	D 74			D 72 Gd			<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	3
003	L 75	D 70	D 80	D 30	D 60	D 70	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	7
004	L 75	D 85	D 85	D 54	D 80		<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	6 1
005	L 62	D 50	D 55	D 60	D 80	D 45	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	1 1
006	D 70	D 90	D 40	D 72 Arth	D 90	D 90	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	6 1
007	L 48	L 70	D 60	L 51	D 60	D 60	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	4
008	L 59	D 63 Pn	D 67	L 63	L 81	D 83	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	7
009	D 50	D 62 Gd	D 47	D 47 Gd	D 32 Typhd	D 76 Gd	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	2 1
010	L 63	D 88	D 62	D 57	D 32 Ch B	D 50	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	2 1
011	L 61	D 75	D 75	D 58	L 85 Db	L 88	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	2 1
012	L 62			D 56 Gd			<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	7 1
013	L 57	D 30 TB	D 66 Gd	L 56	D 30 TB	L 94	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	3 0
014	L 65	D 80	D 80	L 76	D 90	D 98	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	2 5
015	L 80	D 35 TB	D 82	L 88	D 45 Pn	D 60	<div> <div>27</div> <div>25</div> <div>23</div> <div>21</div> </div>	1 1

[illegible]

054	L62	D91	D72	D36 Ca	D66	D73	10
055	L74	D30's	D92 Pn	D56 Acc	D30's	D82	30
056	L46	D	L85	D47		L78	30
057	L71 Arth	D51		D41 Infect	D58 Ca	D67 Pn	13
058	L64	D75	D65	D37 Pn	D78	D84	10
059	D49 Pn			D50 Ca			33
060	D54	D50's	D60's	L67	D60's	D70's	44
061	L53	D31	D69	L55	D50	D63	33
062	D46 Ren			L63	D60's	D80's	44
063	L60 Arth	D75	D74 Ren	D55 TB	D56 Infect	D72 Acc	53
064	L48	D64	D68	L64	D65	D72	21
065	L60	D80	L86	L64	D86	D67	11
066	L60	D66 Pn	D70	L66	D74	D71 Pn	12
067	L56	L81	D54	L59	L98	D82	11
068	L75 Arth	D60's	D70's	D68	D60's	D50's	51
069	D50			D50 Ca			7
070	L63	D76 Collib	D48 Acc	L71 Ren	D50's	D60's Acc	3
071	L87	D87	D40 Infect	D84	D38 Acc	D67	30
072	L69	D72	D83 Ca	D49 Acc	D65	D71 Ren	31

(Unmatched Control Group—continued)

NO	MOTHER	MOTHER'S MOTHER	MOTHER'S FATHER	FATHER	FATHER'S MOTHER	OTHER	PROPOSITUS & SIBLINGS	♂♀
073	L60's	L82	D84	L60's	D83	D70's	() 53 26	2:2
074	L59			L69				1 0
075	L52	D69 Ga	D86	D33 Acc	D55 Ga	D80	53 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	4 2
076	L63	D60's	D50's	L65	D40's	D50's	42	1 0
077	L72	D70 Pn	D72	L73	D35	D76 Pn	59 34 32	2 2
078	L42	L69	D60	L52	L89	D83	2 20 19	1 2
079	L60			D35			2 27 38 34 32	2 3
080	L67	D90	D98	L68 Db	D79	D68	42 38	1 1
081	L55	D50	D80	L60	D80	D85	51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	6 3
082	L54	D82 Acc	D86	L59	D70	D84	50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	3 4
083	L41	L60's	D50's	L52	D70's Db	D70's Db	28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	3 0
084	L74	D70's	D70's	D72	D67	D68 TB	40 37	1 1
085	L55	D83	D75	L60	D50 Acc	D77 Pn	51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	6 1
086	L77			D77 Ga	D83	D81	51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	3 3
087	L68	D87	D87	L68	D60's	D83	51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 0
088	L66	D59	D65	D76	D80	D69	51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 0
089	D42 Infect			L73			51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	2 2
090	L51 Arth	D44	D63	L56	D82 Acc	D72 Ga	51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	2 1
091	L64	D72		D63		D70	51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	2:2
092	L72 Arth	D70's	D74	L76	D90's	D40's TB	51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	4 3

093	L63	D60s	D50s	L65	D88	D85	11
094	D48	D72		D56 Infect			13
095	L62	D84		L64			612
096	D73 Infect			D50			20
097	D42 Infect	D64		L65	D64		210
098	L67	D57 Infect	D84 Acc.	L76	D88 Gg		111
099	L77 Arth	D88	D89	D81 PA	D68		10
100	L68	D88	D50s Asth.	D51 Arth	D60s		31
101	L72	D40 Pn	D60 Acc	L73	D70		24
102	L65	D69 Gg	D30 Acc	D67	D65		112
103	L70	D30s	D30s TB	D79	D50s Gg		12
104	L71	D60s	D60s	D48 Pn	D80s Ren		10
105	D51	D72	D76	L89	D74		111
106	L82	D85	D57 PA	L81	D40s Gg		20
107	D51 Acc	D65	D65	D74	D65		10
108	D70s	D	D	D70s	D80s		30
109	L59 Bh	D60s	D60s	D55	D60s		110
110	L52	D33 TB	D58	D57	D81 Gg		11
111	L65	D73	D70s	L67	D70s		200
112	L70 Arth			D66			61

(Unmatched Control Group—continued)

PROPOSITUS & SIBLINGS ♂♀

FATHER

MOTHER

FATHER

MOTHER'S FATHER

MOTHER'S MOTHER

MOTHER

NO

113	L76	CV	D85	D77	D64	L76	D81	D86	53	52	46	44	31
114	L69		D71		D47	TB			43	42	39		12
115	L78	●	049	D93	D51	Acc	D55	D65	48	41	37		30
116	L75	○	D70's	D80's	D42	Acc	D80's	D70's	48	45	43	40	32
117	L71		D80's	D70's	L73		D70's	D80's	44	42	40		21
118	L70		D86	D56	D55	Pn	D87	D89	51	50	04	Acc 04	30
119	L64	●			D65	CV			39	7			20
120	L60				D42	Pn		D73	43				10
121	D73	●	D62	D78	D75	Ga	D65	D75	42	40	39	37	41
122	D42 Infect		D60	D55	D67	■	D57	D52 Pn	34	32	29	23	52
123	D52 Acc	Ga	D88	D90 Pn	D59	■	D63 Ren	D74	44	42	41		21
124	D63 Ga	Pn	D86	D83 Ga	D59 Park		D61 Pn	D65 Pn	48				10
125	L56		D80	D67	D46	■			32	27	22		30
126	L83		D74	D57	L83		D72	D57	43	41	39	37	10
127	D66	CV		D30's	D82	Pn		D30's	50	31	45	43	33
128	L65		D60's	D60's	L70		D60's	D60's	34	33	32	27	53
129	D36				D44	Db			52				10
130	D64 Liver			D57	D65	■		D65 Pn	44	43	41	40	54
131	L77		D50's Ren.	D60's	L78		D70's	D70's	44	43	41	40	11
132	D77 Ga		D90's	D50's	D80		D90's	19r s	44	43	41	40	41

N 04
[000]
D 11

SHIB N 04

Net 0 42 No 04r

N 04
D 11

N 04

Net 0 42 No 04r

N 04
D 11

133	L63	D65 ●	D76 Pn	L65	D86	D32 Acc	35	36	37	38	39	40	41	42	43
134	L70	D67	D79	L69	D73	D51	4	5	6	7	8	9	10	11	21
135	L66	D50s ●	D86	D60s □	D60s	D60s ▨	46	47	48	49	50	51	52	53	312
136	D56 Ca	D60	D92	D66			42	43	44	45	46	47	48	49	10
137	D60s Flst			D70s □			40 014	41 014	42 014	43 014	44 014	45 014	46 014	47 014	22
138	L76	D78	D76 □	L74			2	3	4	5	6	7	8	9	20
139	L68			L73			40	41	42	43	44	45	46	47	30
140	L74	D81	D66 Ren	D54 Ren	D65 Ren	D92	40 011	41 011	42 011	43 011	44 011	45 011	46 011	47 011	4
141	L73 Arth	D79	D85 Pn	D48 Ren	D68	D74 □	40 025	41 025	42 025	43 025	44 025	45 025	46 025	47 025	5
142	L84	L89	D79 Pn	L66	D55 ●	D85	48	49	50	51	52	53	54	55	30
143	L61 ○	D71 Ren	D80s Pn	D53 TB	D27 ChB	D60s Pn	52	53	54	55	56	57	58	59	10
144	L74	D75	D81	L73	D77	D60	33	34	35	36	37	38	39	40	12
145	D55 ○	D80 ●	D	D60 □	D80	D82 Pn	44	45	46	47	48	49	50	51	21
146	D39 TB	D50s Ca	D	D44 TB	D40s	D40s	32	33	34	35	36	37	38	39	41
							32	33	34	35	36	37	38	39	32

(Unmatched Control Group—concluded)

APPENDIX D

Diet Record

QUANTITIES of all foods drugs tobacco and alcohol ingested were recorded by the interviewer on the accompanying form The amounts were then extrapolated to a weekly basis for the final recording and analyses For the coronary group records were made of food habits both prior to and after the coronary episode For the controls the usual diet was listed and any changes were noted

MASSACHUSETTS GENERAL HOSPITAL

Coronary Research Project No 6

name	series	sex
age	(no)	(Diet Card)
(1) Beef all forms	(20) Eggs all forms	(39) Liquor
(2) Veal all forms	(21) Milk (per glass)	(40) Cigarettes
(3) Lamb all forms	(22) Buttermilk	(41) Pipes
(4) Mutton all	(23) Cream	(42) Cigars
(5) Pork all forms	(24) Cheese all	(43) Digitalis
(6) Bacon strips	(25) Nuts all ex 26	(44) Thyroid
(7) Brains all	(26) Peanuts	(45) Sedatives
(8) Liver all	(27) Peanut butter	(46) Vitamins
(9) Sweetbreads	(28) Chicken	(47) other
(10) Frankfurts etc	(29) Fowl ex 28	(48) Preferences
(11) Specialty meat	(30) Beans	(49) Aversions
(12) Salmon Swordfish	(31) Coconut	
(13) Halibut Whitefish	(32) Candy	
(14) Lobster crab etc	(33) Popcorn	(50) Allerges
(15) Scallops oysters	(34) Coffee	
(16) Fats tallows	(35) Tea	
(17) Butter oleo	(36) Cocoa	(51) Sugar protein carbo-
(18) Oils dressings	(37) Beer	hydrate or fat?
(19) Vinegar	(38) Wine	

directions indicate measure (G-glass S-serving P-pat, O-oz.) and unit of time (Wk Mo Yr) preferably on weekly basis viz., Milk 14G-w O-rare or never

APPENDIX E

Summary of Case Histories

Case no	Nationality	Age	Date of arrest	Place of arrest	Alibi	Statement before & after	Complete or partial	Time of arrest	Refused
001	Italian	35	1/22/2 8:00 am	naples on street	1st p. 1st on bus	none	substantial part	severe	left elbow & fingers
002	Irish	40	6/12 1:30 p.m.	none	at my bank after 5 p.m.	lawyer	substantial part, vomiting	severe	clavicle
003	Irish	39	11/26/40 8:00 p.m.	none	walking	none	substantial part	moderate	upper abdomen
004	Irish	15	5/12 12:15 p.m.	red garden for 4 yrs. for 10 min or heavy	nothing	unknown	substantial part	severe	forearm, elbow
005	English	35	7/1/2 11:00 noon	my effort at all or 1 value but drinks or eating heavy meals	nothing	truck 4 yrs	substantial part	moderate	elbow, wrist, shoulder
006	Irish	12	12/12 1:00 am	headache and pain in stomach heavy meals	nothing	contractor & bus-ness agent for double transporter	substantial part, swollen, collapsed, vomiting	severe	both arms
007	Italian	27	2/1/2 2:00 am	disposal on street and	nothing	road grade	substantial part	severe	left arm
008	Irish	25	1/45 10:00 p.m.	severe heat and on symptoms swollen, above to both arms and in side	nothing	nothing to wear or a schuman, then clothing there	substantial part	severe	arm
009	French	35	11/7 7:30 am	heat & swelling in the wrist after he was shot, and got out	nothing	in the 20 am	substantial part	severe	elbow, wrist, hand
010	Irish	40	12/30 2:00 p.m.	none	at home	truck 4 yrs	substantial part	severe	arm
011	Italian	34	1/4/45 12:30 am	none	preparing budget for movement	empty office now abandoned	substantial part	severe	upper abdomen
012	Irish	34	9/1/45 2:30 p.m.	disposal on street for 1 yr	nothing	garage for 1000 to 1000 of the	substantial part	severe	both arms
013	Irish	3	9/23/45 8:00 am	none	nothing	truck driver now maintenance man	substantial part	severe	both arms

At the time when the report was submitted, December 1, 1946. For paragraph on all December 1 & 2 see Appendix F.
 1. Indicate report or history of involvement.
 2. Normal roentgenogram.

Examination	Fluoroscopic & X-ray Findings	C.T. ratio	Location of defect	Rt. Am.	C. valvular defect	Other ECG find.	Heart base size	Change in d.	Recurrent	P. conduction time delay & doublet
3 sec. above 10/10	not remarkable, 2 (4/7) 3 19/42, 4 11/7	12 31	post?	N.S.R.	none	none	MOH base 5 in.	yes	no	apnea & dyspnea on effort
1 in.	70-80 slight heart transverse diam. of heart enlarged left vent.	15 3 31.2	post?	N.S.R.	none	none	base 9 in., de-aorta 6 in.	yes 2 in. apnea, fluid foods	no	limited exercise
1 in.	2.25 40 N.R.S.	15 31.5	post	N.S.R.	none	none	base 10 in.	yes low cholesterolemia	yes (1941) 54	no strenuous activity
1 in.	2 1 49 pulsations diam. along left heart margin	16 32	post.	N.S.R.	none	none	base 6 in. aortic max.	yes later big	yes 1 44	limited exercise
2 sec.	3 1 49 pulsations diam. along heart always bilateral	1 7 30	post.	N.S.R.	none	none	none	yes low fat	no	apnea, shortness of breath
1 in.	2.25/ 9 pulsations diam. short border left vent. enlarged left vent. none	14 6 32.5	post.	N.S.R.	R. B. B.	L.V.H.	base 10 in. aortic 3 in.	yes low C	no	apnea on exert and exert, heavy work
1 in.	3/17 9 not remarkable	1 7 35	post.	N.S.R.	none	none	base 10 in. aortic 3 in.	yes low C	no	apnea & palpitation on exertion
2 in.	49 slight prominence of left vent.	15 30.5	post.	N. R.	none	L.A.D. L.V.H. and strain	base 10 in. aortic 3 in.	no	no	apnea on exert, effort
1 1/2 in.	3 70/ 9 heart rate very rapid pulsations of small amplitude	15 30	post.	apnea tach and C	none	none	base 10 in. aortic 3 in.	yes no eggs	no	apnea on exert to exert, no exert
2 in.	3/ 40 N.R.	35 3	post.	N.S.	none	L.A.D.	base 10 in. aortic 3 in.	yes	no	none
2 in.	2 1 48 heart transverse diam. enlarged left vent. representing old scar	1 30.5	post.	N.S.R.	none	none	base 10 in. aortic 3 in.	yes low cholesterolemia	no	apnea, palpitation on effort
2 in.	3 49 left vent. mod. enlarged, transverse shows calcification in trans portion (7, N.R.)	1 5	post.	N.S.R.	none	none	base 10 in. aortic 3 in.	yes low fat	yes 94	apnea, shortness of breath
3 in.	3 calcification seen in apical region of heart suggestive of pericarditis, enlarged left vent.	30	post.	N. R.	none	none	base 10 in. aortic 3 in.	yes	no	none

CASE HISTORIES

Date	Fluoroscopy & x-ray find	CT no	Location of infar	Rhythm	C duration of inf	Oh ECG find	H P ha em	Change of diet	Reurrence	Patient's complaints & disability
1 hr	1. 49 pulmonary div. along left border enlarged left vent.	1 33	post.	NSR.	partial AV block PR int. 0.2	none	none but 31.2 mm. tall as ac	yes on f	no	recor. pain in chest & lower arm
2 hrs	1 70 48 N.R.	15 23.5	post. ↑	NSR.	none	L.V.H. & tris	loop 6 ka. spec vs 6 ka.	no	yes 75 inactive (1943)	clin. norm. activity
3 hrs	1 54 enlarged left vent	16 30	an	NSR.	none	none	loop 8 ka. spec vs 2 mm.	no	yes 1929	partly crippled by gout
12 hr	1 56 48 left vent enlarged, aorta tortuous, lung fields margin bronchectatic	14 29	post. ↑	NSR.	none	none	loop 7 ka.	yes low caloric	yes	dead of myocardial infarction
1 sat.	not available 1 44 9 1 46, 4 30 8 17 49	12.2 2	an	NSR.	none	none	HIGH 1 d vs. spec. vs ka.	yes clin. no other is	no	lim. ac vs sports
2 hrs	5 11 48 N.R.	3 17.5	post. ↑ ant.	non-tac y-cardi	R. B.B.	occult P.V.C.	no spec. active 1	no	yes 9 33/46	ypnea & an as an effort
2 hrs	2. 18/49 N.R.	13 8	post.	NSR.	none	loaden to R.A.D.	loop 8 ka. spec vs 7 mm.	no	no	signs on effort
3 hr	3 11/48 N.R.	15 34	post. ↑	NSR.	none	none	loop 1 spec.	no	no	best pain, ypnea on exertion
4 hrs	8 40/ 7 N.R.	—	—	NSR.	none	no	no spec vs ka.	yes low cholesterol	no	n. stren. activity
5 hr	—	—	an	NSR.	none	L.A.D.	loop 3 spec. spec 3 mm.	yes low f	no	accor. best pain on effort
7 hr	1 1/4 49 N.R.	5	post.	un-brad and	no	none	exp 1 ka. ka loop spec.	no	no	norm. clin. signs, norm.
1 hr	5/17 N.R.	15 5 3	post.	NSR.	none	none	exp 1 ka.	yes low caloric	yes 5 7	none
18 min.	5/17 1 left vent already enlarged but hypertrophy not noted, pulmonary vas. engorged	10 7 25	—	NSR.	none	none	HIGH 7 mm. spec vs	yes spec. f	no	dyspnea, palpitation on exertion
1 hr	—	—	post.	NSR.	none	none	loop 7 ka. spec. spec spec.	yes low cal. low cholesterol	yes 2. 5 1	dyspnea, no physical exertion
2 hr	5/21/49 slight over in AP diam. of chest	19 3 5	an	NSR.	none	none	no	yes low ka	no	none
3 hr	1 7/48 left vent enlarged, pulmonary shadow along border left vent., representing thinned wall myocardium not anycardi	2	ant.	NSR.	L. B.	L. R.	loop 6 spec. active 3 mm.	yes low cholesterol, salt free	yes 64 7	limited work, no exercise
6 hr	4 24 48 N.R.	13 5 32.5	post.	NSR.	none	none	loop 2 spec. inactive spec.	yes low fat & cholesterol	no	—

Case no.	Nationality	Age (yrs.)	Date of onset	Following complaint	Activity at onset	Occupation before & after	Character of onset	Duration of pain	Relief
031	Irish	28	3/44 3:00 p.	none	climbing	laborer, stevedore	subacute pain	moderate	none
032	Irish	40	8/9/47 12:30 a.m.	pain, arms & W	climbing	loc. work	subacute pain	severe	arms, legs
033	Irish Irish	36	1/48 7:00 p.m.	supra-patellar W rt	climbing in deep mine	mining	subacute pain	moderate	left arm & eye
034	Irish	55	12/46 8:00 p.m.	marked weight gain, marked growth of hand, feet & legs, C10 per ton	climbing & coal	housewife	chronic pain	severe	total
035	Old American	40	11/17/47 7:00 p.m.	3 weeks of and pain, 1 yr prior onset and dyspnea	climbing in bed	machine operator in power machine inspection	subacute pain, chafing	severe	arms & hands
036	Irish	36	3/45 1:30 p.m.	none	climbing to work	laborer, miner, no weight & shift	subacute pain	moderate	none
037	Irish	31 & 12	2/25/49 1:30 p.m.	dizziness, 1 day, dizziness no weight & through lower in neck	climbing, work	laborer, miner	subacute pain	severe	none
038	Irish	3	9/23 > 8:00 m.	none	climbing	mining	subacute pain, infection, C10	severe	none
039	Old American Irish	16	1/1/47 8:00 p.m.	1 yr in chest, pain in arms with weight & no cold, occasional	climbing in mine	miner	subacute pain	severe	none
040	Irish Irish	55	10/1/44 3:00 p.m.	1 yr, dyspnea on stairs 1 yr	climbing in pit	laborer in hotel	subacute pain	severe	none
041	Irish	40 11/12	1/12/46 8:00 m.	indigestion, some pain, 1 yr	climbing, home work	mining	subacute pain, chronic p. 1 yr	moderate	none
042	Irish	18	11/25 37 7:00 m.	none	climbing in mine, no work	mining	subacute pain, indigestion	moderate, then severe	none
043	Irish	37	8/1/42 10:00 p.m.	supra-patellar W	climbing in mine	laborer, miner in mine	subacute pain	severe	left arm & hand
044	Irish	37	1/17/44 2:30 a.m.	none	climbing	mining	subacute pain	severe	none
045	Portuguese	36	10/3 8:00 p.m.	none	climbing in mine & office work	physician	chronic & severe	severe	none
046	Irish	34 & 12	4/46 7:30 m.	none	climbing in mine	laborer	chronic, hand, foot, numbness, left arm	severe	numbness, left arm
047	Old American	54	12/17/46 2:00 p.m.	dyspnea 2 yrs, before & after in arm, shoulder, stomach	climbing in mine	mechanical engineer	subacute pain, numbness in arm & shoulder	moderate	arms & shoulder

CASE HISTORIES

Days	Fluoroscopic & x-ray findings	CT ratio	Location of infar	R. dist	Conduction defect	Other ECG findings	R. heart or	Cham f dist	Recurrence	at onset & ability
2 hrs	10/22/47 left vent. enlarged	1.22	yes	N.S.R.	impaired intraventricular regular conduction 0.11 sec	L.V.H. & strain	h. no. k	yes, not f. m. low h. lateral	1/43	dead 1949
1 hr	1/22/77 calcification both apices, left vent. enlarged	1.53	no	N.S.R.	none	none	loop 6 k. h. no. 6 m. no	yes low indicator f	no	occasional chest
3 hrs	1/1/49 slight prominence of left vent., low fields low	14.31.5	yes	N.S.R.	none	none	no 2 k. h. no. 5 k.	yes low f. & cholesterol	no	at 11 & ext. stress
1 hr	12/7/67 not remarkable	14.28.5	post.	N.S.R.	R. BBB	none	none observed ant. of housework	yes low side	no	pain in ft. arm, heart & pal. 100 iron, shortness
7 hrs	1/48 N.R.	29.5	no	N.S.R.	partial A-V block	none	loop 5 1/2 k. h. no. 7 dist.	no	no	epilepsy & seizures and rashes
2 hrs	10/28 slight prominence at apex of left vent.	14.5.30.5	post.	N.S.R.	none	L.V.H.	none, can work	yes low f	yes 946	at 14 posterior dal 300 tabs. norglycine per
4 hrs	1/28/ N.R.	1.30.2	ant.	N.S.R.	none	none	loop 6 k. h. no. 3 m. no	no	no	none
3 hrs	1/4 aortic tortuosity, enlarged left vent.	18.3	yes f. an	none P.V.C.	Q S 1	LAD L.V.H. & strain	loop 6 k. h. no. 3 m. no	no	yes 9.2	dead 1948
1 hr	1/1/9 pulsations dim. along border of left vent., prominent aortic arch	1.3	no	N.S.R.	none	none	loop 2 m. no. 3 m. no	no	no	none
1 hr	1/2, N.R.	13.5.35	no	N.S.R.	none	none	loop 9 k. h. no. 3 m. no	yes low cholesterol	no	none
12 hrs	11/1 7 N.R. 1/29/48 N.R.	39.29	no	N.S.R.	none	none	MGH 5 k. h. no. 3 m. no	yes low cholesterol	no	dim. stress, sparse
—	5/9/48 N.R.	12.4.27.5	ant.	N.S.R.	none	none	loop 4 k. h. no. 3 m. no	yes low cholesterol	no	none
1 1/2 hrs	1/20/ N.R.	1.5.30	ant.	N.S.R.	none	none	loop 3 k. h. no. 3 m. no	yes	yes 1	angina on effort
1 1/2 hr	7 enlarged left vent.	3.5.28	post. f	N.S.R.	none	none	loop 5 k. h. no. 3 m. no	no	no	can walk fast, run, climb stairs
—	1/13 slight prominence at apex of left vent.	1.3	post.	N.S.R.	none	occasional P.V.C.	loop 4 k. h. no. 3 m. no	yes high	yes 946	all activities limited
24 hrs	1/25 chest clips along both sides of lower dorsal spine	13.32	post.	N.S.R.	none	none	loop k. h. no.	no	no	can climb stairs
7 hrs	12/3 7 not remarkable except C.T. ratio enlarged left vent.	1.27	ant.	N.S.R.	— — — —	L.V.H.	loop 2 k. h. no.	yes	no	dead 7-48

Case no.	Age	Sex	Date	Time	Present complaint	History of illness	Illness onset before date	Current symptoms	Duration (mo)	Examination
048	Old American	46	10/12	4/47 1:00 a.m.	supine dyspnea 3 yrs.	sleep	heart	subcostal pain	severe	none
049	Old American	40	1/14/47	7:00 p.m.	has p no d yrs. on ev. p commonly treated for Biering disease	is smoking	back	palmer internal pain, nausea, vomiting	severe	left arm, upper abdomen
050	Old American	33	4/17/46	11:00 p.m.	none	nothing but none smoking	is not sure	subcostal p at	moderate	left arm & shoulder
051	Italian	36 & 12	5/3/7	1:00 p.m.	undigested several 3 before, nervous tension, 5 yrs	eating	back drive	nausea, vom. ind. cramps, subcostal pain	moderate	fatigue
052	Old American	35 & 13	1/20/5	8:00 p.m.	thyroidism 1935	works in office	larynx	nausea, yncopal pain	mild	none
053	Italian	23	10/9/46	5:30 p.m.	none	get 3 yrs in bed in hospital	worked over by day	subcostal pain	moderate	nausea, vom. ind. back, is
054	Jewish	26	10/1	12/21/47 9:00 p.m.	1 yr 5 mos. prob. in chest on	also 3 mos. smoking	SV 30 on for no selection	is very present in heart	mild	none
055	Irish	33	10/24/5	10:00 a.m.	gone 3 months before	living around back no shop	nausea on for for me	distention, subcostal pain	moderate	none
056	Irish	40	1/19/5	2:30 p.m.	3 yrs. before	change full	hearted now teacher (then try)	heart in chest, chest p	moderate	left shoulder
057	French Irish	35	8/1/39	8:00 a.m.	none	be in	back	subcostal pain	severe	left shoulder
058	Irish	38	7/21/40	12:00 p.m.	no in left arm for 1 yr	no thing in chest	also 300 gr	subcostal pain	moderate	left arm
059	Danish	41	11/10/44	2:00 p.m.	dyspnea and indigestion 4th to 1 yr before	and talk in chest	back pain	nausea, subcostal pain	severe	upper arm, throat
060	Italian	33	11/15/5	1:00 p.m.	none	lyte touch football	manage industrial film	internal & upper abdominal pain	severe	none
061	Jewish	45	10/12/40	2:00 p.m.	none	going up hill	active thermometric factory	is 11 present in heart	moderate	left arm
062	Italian	29	1/13/4	12:00 a.m.	dyspnea and weight on effort	none during heart's hour	brassier now unemployed	subcostal pain	severe	left arm, throat, back
063	Irish	39	1/20/4	2:00 a.m.	1 yr for few days	white and dry the coffee	nothing after tea	subcostal pain, nausea, fatigue	severe	through to back, arm to chest
064	Jewish	39	12/13/46	8:30 a.m.	heartburn for 2 yrs.	working in factory	labour	heartburn, profuse perspiration	moderate	none
065	Danish German	27	5/13	9:15 5 10:30 a.m.	occasional pain in left arm associated with stress, nervous	walked 1/2 mile carrying heavy suitcase	subcostal pain	severe	none	none

CASE HISTORIES

Age	Fluoroscopic & x-ray find	CT scan	Location of lesion	R. arm	Conduction & pac	Other ECG find	Temp or home care	Change of diet	Response	P. sent to hospital & disability
1 yr 4 mo.	1 x 48 N.R.	—	no	N.S.R.	none	R.A.D.	home	yes low cholesterol	yes 1/48	dead 1/48 MCH under stud. & obs.
1 yr	1/1 48 N.R.	12.8 31	post.	N.S.R.	none	none	keep 4 wh. capsules 2 mos.	yes low sat. & cholesterol	yes attacks then none	dead 3 7/9
1 yr 11 mo. 2 mo.	1/27 48 N.R.	12.5 30	ant.	N.S.R.	none	L.A.D.	keep 1 pr capsule 3 mos.	no	no	none post-tum stress sports
1 yr 4 mo. 8 mo.	1 50 48 area of increased density left interpos.	13.8 32	no	N.S.R.	none	none	home 6 ka.	yes low 3 cholesterol	no	acute mild subventricular pain
1 yr	2 7 48 2 8/49 nodules by enlarged left vent.	15.5 33	(30) pos (new)	N.S.R.	none	none	home 1	no	yes 9/7	slim, stren. sports
1 yr	5 11 48 N.R.	13 32	post.	N.S.R.	none	none	home after 10 0 ka.	yes ill cholesterol	no	slim, stren. sports
1 yr	5/15/48 sl. gh prominence of left vent. no post.	15.2 28.6	no ?	N.S.R.	none	L.A.D.	home 4 ka. 4 days, inactive too	no	no	less easily ex. exercise
1 yr	2. 3/48 sl. gh accentuation of vascular markings	14 30	no	N.S.R.	none	L.A.D. L.V.R.	keep 4 ka. home 1 1/2 ka.	no	no	no glycerine daily for asthma
1 yr	2 1 8 N.R.	12.5 31	pos	no too y arch	none	none	none	no	no	fatigue, probable psychological
1 yr 6 mo.	15 48 sl. gh prominence of left vent. compressed.	4 32	post.	N.S.R.	none	none	exp at 10 1 pr	yes no (15 low cholesterol	no	slim, stren. sports
1 yr 6 mo.	3 1 /48 left vent. enlarged, vascular markings prominent	6.5 31	no ?	N.S.R.	none	none	keep home inactive 3 mos.	no	no	slim, stren. sports
1 yr 6 mo.	2/24 48 8 aorta dilated & tortuous. enlarged left vent.	16.5 3 5	pos ant.	N.S.R.	none	none	home inactive ant.	yes low fat	yes 1 7	dizziness, dyspnea
2 yrs	3 3 sl. gh enlarged left vent.	3 2 30.5	pos	N.S.R.	none	none	keep 4 ka. inactive 1 pr	yes low fat	no	slim, stren. sports
2 yr 6 mo.	3 6 ph tortuous aorta	13 30.5	post.	N. R.	none	none	home ant.	no	no	slim, stren. sports
3 7 mo.	3 N.R.	5	post.	N.S.R.	none	none	keep inactive 3 pr	yes low cholesterol	—	more angina on effort, dyspnea
4 yrs	none obtained	—	post	N.S.R.	none	L.A.D. 30	home 1 mo.	no	yes	dead 3 7/9 of myocardial infarction
4 yrs	3 1 48 prominence on left vent.	—	post.	N.S.R.	none	none	keep 5 wh. home 2 wh.	yes low sat.	yes 10 11	dead 3 1 09
4 yr 6 mo.	3 48 apparent prominence in left vent.	3 30.8	post.?	N.S.R.	none	none	keep 6 wh. inactive 3 mos.	yes low cholesterol	no	none

Cas no	Nationality	Age at onset (yrs.)	Date & time	Preceding complaints	Activity at onset	Occupation before & now	Complaint at onset	Degree / pain	Location
066	German	36	4/18 7 7 00 p.m.	chest pain & aching in both arms while working	working as automobile	auto mechanic	subclavicular pain	severe	both arms
067	German Ea lah	39 1/12	3/1 44 6 30 a.m.	none	at bed	farmer	subclavicular pain	severe	arms, back of neck
068	French Br tak lahm	39 11 12	1/7 7 1 00 a.m.	dyspnea on climbing steps or walking rapidly	at work at office desk	electrical engineer	subclavicular pain	moderate	forearms
069	English French	35	12/9 43 5 00 p.m.	pain in arms on exertion & none before	walking	dentist	subclavicular pain with radiation to arms	moderate	arms
070	Jewish	36 10 12	11 15/ 2 3 00 p.m.	pain radiating down left arm after day's work	walking	radio repair operator now salesman	sternal distress, no pain for 30 min. after 30 min.	severe after 30 min.	left arm from elbow to wrist
071	Italian	31	7/9/46 4 00 p.m.	onset on exertion with radiation to arms 2 yrs.	at yard built	tailor now laborer	subclavicular pain	moderate	arms
072	German	34	7 11/ 7 2 00 p.m.	none	working in garden	typewriter parts and maintenance	subclavicular pain, heartburn, dyspnea	moderate, severe	arms
073	Old American	37	12/27 46 3 00 a.m.	adaptation for 1 yr chest pain on exertion associated with dyspnea	sleeping	sales representative	subclavicular pain	severe	left elbow nerve distribution
074	Ital	40	1 14/46 3 00 p.m.	none	long on toilet, read ng	used car dealer	subclavicular pain	severe	none
075	British Isles	31 8/12	8 6/40 9 30 a.m.	none	lifting heavy objects	electrician	radiation, subclavicular pain	moderate	upper abdomen
076	Jewish	38	4 9 46 30 a.m.	onset on effort, 100	lying in bed	mechanic	heartburn, subclavicular pain	moderate	arms, back
077	British Isles	3	5/2 7 00 p.m.	severe pain in left arm while driving car 2 years before	lying in barber shop	several years operator	subclavicular pain	severe	left arm and fingers
078	Jewish	3	11 13/ 8 9 30 p.m.	dyspnea on climbing 1 flight of steps	sleep, talking	salesman, desk work	subclavicular pain	severe	none
079	British Isles Dutch	39	6-27/3 5 00 p.m.	dyspnea while playing tennis	laying tennis	operator	subclavicular pain, dyspnea	very severe	none
080	Jewish	38	7 13/ 7 3 00 p.m.	high dyspnea prior to arm attack	driving automobile	physician, home based work	subclavicular pain	severe	none
081	Irish	33	1 28 46 00 p.m.	none	riding on elevator	pusher now watch maker	heartburn, subclavicular pain	severe	to right hand and thumb
082	Austrian	36 5/12	1- 6 6 00 p.m.	angina 2 yrs. on strenuous work or excitement	sleeping	mechanic	heartburn, subclavicular pain, sweating	moderate	none
083	Irish	34	7/23 49 11-00 p.m.	none	digging tubs	tailor now clerk and salesman	subclavicular pain, dyspnea	severe	none

Onset	Fluoroscopic & x-ray findings	CT value	Location of infarct	Rhythm	C wave at 1 sec	Other ECG findings	Heap or home use	Change of diet	Recurrence	Heart complaints & disability
1 hr.	3/18 48 N.R.	12.8 79	ant.	N.S.R.	none	none	heap 1 wk., heart 1 mo inactive 2 mos.	no	no	none
1 hr.	3/21/48 N.R.	13.5 30.3	an	N.S.R.	none	L.A.D.	heaps 6 wk., inactive 1 yr	yes low f	no	none
1 hr.	3/24/48 N.R.	4 33	post.	N.S.R.	none	none	heaps 5 wk., inactive 5 wks.	yes	no	none
several days	3/24 48 N.R.	12 29.2	post.	N.S.R.	none	none	none	yes low cholesterol	yes	dead 1/10/48
1 hr.	3/1 48 N.R.	1 31.5	post.	N.S.R.	none	none	heaps 6 wk., not very good.	yes low quantity	no	slight stress, sports only
hr.	7/13/48 slightly enlarged left vent.	1 2 6	post.	N.S.R.	none	none	none	yes low cholesterol	yes	dead 1948
1 mo.	7/1 48 N.R.	5 74	an?	N.S.R.	none	none	none	yes low cholesterol	no	none
1 hr.	7/1 48 N.R.	31	post. & ant.	N.S.R.	none	none	heaps 3 wk., inactive 6 mos.	yes low caloric	yes 1 1 00	occasional heart pain, sleep, all exercise
7 hrs.	7/21/48 N.R.	3 30	post.	normal broad cardiac	none	none	heaps 2 mos., inactive 77	yes low cholesterol	yes 9 44	occasional heart pain on exertion, last episode
min.	7/21/48 slightly enlarged left vent	3 22	ant.	N.S.R.	none	none	heaps 1 mo inactive 600	no	no	slight sports, no other complaints
min.	8 48 N.R.	—	ant.	N.S.R.	none	none	none	no	no	none
5 hrs.	72 48 slight increase in stress, distal, enlarged left vent	26	ant?	N.S.R.	none	L.A.D.	heaps 2 mos., inactive 600,	yes low cholesterol	no	chest pain on exertion or after over exerting
0 hrs. mild oxygen was van	5 6 48 enlarged left vent, sh tortuosity of aorta	32	ant?	N.S.R.	none	none	heaps 6 1/2 wk., inactive 6 mos.	yes low fat	no	painstaking, dyspnea on exertion
hrs.	5 paradoxical pulsation along border of left vent., ant. border apex	12.3 30.3	ant?	N.S.R.	none	none	heaps in bed, inactive 3 mos.	no	yes	elbow to wrist sports
7 hr.	5 48 severe heart without obvious thoracic	6.5 3	post.	N.S.R.	none	none	heaps 3 wk., inactive 600,	yes low choline, food	no	occasional pain & pain after exertion
12 hrs.	7 1/48 N.R.	—	post.	N.S.R.	none	none	heaps 3 mos.	no	no	moderate fatigue
3 hrs.	6/24 48 pleural thickening left costophrenic angle; respiratory motion 2nd left rib for old emphysema	1 2 31.5	post.	N.S.R.	none	none	heaps 2 1/2 hr., home 3 wk.	no	no	heart chest pain on exertion
24 hrs.	5 3 48 severe heart, slight prominence of left vent.	5 30	post.	N.S.R.	none	L.A.D.	heaps 2 mos., inactive 600,	yes low cholesterol	yes	

APPENDIX F

Follow Up Study of Coronary and Unmatched Control Groups

Coronary Group

A STUDY was made of the status on December 31, 1953 of the original 100 patients with coronary heart disease * The results were as follows

Status of 100 patients on December 31 1953 (97 male 3 female)

	<i>Dead</i>	<i>Alive</i>	<i>Whereabouts unknown</i>
Men	21	62	14
Women	2	1	1

All the deaths of both men and women resulted from coronary heart disease

Duration of survival following initial coronary episode in the 21 men known to have died

<i>Duration of survival in months</i>	<i>No of men</i>
0- 12	0
13- 36	5
37- 72	5
73-108	5
109-147	6

It will be observed that for the 21 men who expired the average survival period following the initial coronary episode was 6 years and 6 months with a range from 16 months to 12 years and 3 months The 2 women who expired survived 7 months and 49 months respectively

*The authors are indebted to General Lewis B Hershey Director National Selective Service System for his cooperation in tracing members of both coronary and control groups

Survival period following initial coronary episode in the 62 men known to have survived

<i>Duration of survival in months</i>	<i>No of men</i>
42-60	4
61-72	11
73-84	10
85-96	10
97-108	7
109-120	3
121-132	5
133-144	4
145-156	2
157-168	2
169-180	1
181-192	3
193-204	1
320	1

The average survival period to December 31 1953 was 8 years and 7 months with a range from 4 years and 7 months to 26 years and 8 months (The median survival was 8 years and 7 months)

Main symptoms among the 62 men known to have survived

	<i>No of men</i>
Main symptoms	
dyspnea on exertion	13
residual angina pectoris	22
indigestion only	1
Activity	
full day's work	57
partially disabled	5

The 1 remaining woman carried on her household duties

Unmatched Control Group

Responses from 130 of the 146 men who comprised the unmatched control group revealed that as of December 31 1953 all were working. Seven had symptoms which may be interpreted as angina pectoris while 4 others had left precordial pain of non specific character. One had experienced a myocardial infarction.

As a group the unmatched controls had not undergone any severe illnesses. Three had had major elective surgery with complete recovery, two minor surgery with no dire consequences.

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